VOLUME 10 MAY 1961 NUMBER 2

AUSTRALASIAN ANNALS OF MEDICINE

Journal of The Royal Australasian College of Physicians

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Does a training in medicine or science fire the imagination? Of course it can and should, but too often it does not. Yet without imagination no really fruitful work is done. Perhaps instruments and equipment are of ever-increasing importance, but their value can be over-estimated. To have watched Faraday at work fixing a magnet inside a coil of wire would have given no inkling of his genius. His unique contribution to science was a leap of imagination: to conceive a field of force between wire and magnet. "What this state is", he wrote, "cannot be declared." A field of force has no material basis, but this did not matter, for as soon as he began to think, wire and magnet were forgotten. Faraday entered a world of abstraction. "The mutual relation of electricity, magnetism and motion", he wrote, "may be represented by three lines at right angles to each other." Sheer symbolism; and yet from this stems the Snowy Mountains Hydro-Electric Scheme.

Science abstracts from nature shape from a crystal, pressure from a gas, resistance from a wire, and transforms these abstractions into symbols. The realities of science are not wire and magnet, but current and electromotive force; not glassware and pumps, but pressure and volume; and when grants for instruments and equipment are sought, the question that must be asked is what end they will serve. Abstraction, symbolism and imagination are the real tools of the scientist, and the pattern of his thought is akin to that of the poet and the artist, for his tools are identical.

A handbook of science in 1892 stated that "the hard and stony path of classifying facts and reasoning upon them is the only way to ascertain truth. It is the reason and not the imagination which must ultimately be appealed to. The poet may give us in sublime language an account of the origin and purpose of the universe, but in the end it will not satisfy our æsthetic judgement, our idea of harmony and beauty, like the few facts which scientists may venture to tell us in the same field." In other words, "The Sea Around Us" by Rachel Carson is more satisfying than *The Rime of the Ancient Mariner* by Samuel Coleridge. It will be said that the two works are not comparable. Miss Carson has classified facts about the sea and reasoned upon them, and in presenting her subject in a popular way has not offended against the canons of science.

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In the British Museum is a small manuscript volume of 90 pages. It is a notebook kept by Samuel Taylor Coleridge over a period of three years from 1795 to 1798, the years which embrace the growth and flowering of his genius. The notebook contains suggestions jotted down chaotically from Coleridge's absorbing adventures among books; and from the notebook came *The Rime of the Ancient Mariner* and *Kubla Khan*. In a remarkable book, " The Road to Xanadu ", John Livingstone Lowes traces " the operations of that shaping spirit of imagination which, moving through the welter, fashions its elements into lucid and ordered unity ". It is a thought that such a phrase could be used about the creative scientist as well as about the poet, and that the term, " the disciplined imagination ", used by Karl Pearson in " The Grammar of Science ", is applicable to both.

Coleridge was an omnivorous reader with what he described as " a tenacious and systematizing memory ", but in addition he had the habit of verifying references. He read Captain Cook's narratives of his voyages, and it is probable that he came under the influence of William Wales, who taught mathematics at Christ's Hospital when Coleridge was there. Wales had been astronomer and meteorologist on the *Resolution*. He read Joseph Priestley's " Opticks ", and a passage in it about shining fishes gave him a reference to the *Philosophical Transactions of the Royal Society*, where he read an account by a Jesuit missionary, Father Bourzes, on " Luminous Appearances in the Wakes of Ships in the Sea ". In the same volume is a communication to Mr. Waller of the Royal Society from Cotton Mather of New England, and in it is written: " There is a Tradition among them, that in November, 1668, a Star appeared below the Body of the Moon within the Horns of it." In *The Rime of the Ancient Mariner* one reads:

> Till clomb above the eastern bar
> The Horned Moon with one bright star
> Within the nether tip.

Only the fringe of Coleridge's reading has been touched here, but a scientist, a Jesuit priest, and a sailor, Captain Cook, all contributed to the raw material of:

> They moved in tracks of shining white
> And when they reared, the elfish light
> Fell off in hoary flakes.

This raw material, along with a vast amount of unrelated matter, was dropped for the time being into the deep well of the mind, to be dredged up when the time came and transmuted into *The Rime of the Ancient Mariner* by what Coleridge called that synthetic and magical power, the imagination. He went on to speak of " the streamy nature of association which thinking curbs and rudders " until out of chaos comes order and beauty.

C. P. Snow has described the scientific edifice of the physical world in its intellectual depth, complexity and articulation as the most beautiful and wonderful collective work of the mind of man, and he predicts that the scientists have the future in their bones. Much of the concern of the modern physical scientist is essentially not of a nature to be directly known to sight, touch or hearing, and his view of the universe is a deliberately woven structure of ideas which radically diverges from sense perception. It is also worth noting that we have reached the limit of knowledge that can be gained by sense perception in medicine. The future lies with the scientist, and it is difficult to share Snow's concern with the lack of comprehension of the scientific culture by what he terms the non-scientific or literary culture. What does matter is that the scientist should comprehend the supreme importance of the shaping spirit of imagination, and for this reason alone he has much to learn from the non-scientific culture. *The Rime of the Ancient Mariner* in its intellectual

depth, complexity and articulation is also a work of wonder and beauty, and an example of a problem that began with an idea which plucked from the deep well of the mind the material required for its purpose, selected and shaped it by the disciplined imagination and set forth the result in the form of a poem. A scientist should appreciate this as much as C. P. Snow appreciates the scientific edifice of the physical world. What is more, he would be able to demonstrate to his students not only the sources of Coleridge's works, which embraced the writings of Joseph Priestley and Humphry Davy, the *Philosophical Transactions of the Royal Society*, John Hunter on the anatomy of the whale, Cook's " Voyages " and countless other books, but also how from chaos the imagination frames a thing of beauty.

This brings us back to the head of Medusa . . . Is imagination an innate quality in all, that dies untimely in childhood in some, that perishes in adult life increasingly for lack of nurture, and that may be lacking even in some who choose the scientific culture ? Maurice Arthus spoke of a clear and limpid imagination as a mental quality possessed in various degrees, which may be improved constantly by the exercise of iron determination. This and a spirit of independence and originality he regarded as the requisites for scientific work :

> Their suppression or their absence is why the scientific work of our young people to-day is often so dull, so colourless and so sad. It lacks the characteristics that are those of robust health and a free life, namely spontaneity and unexpectedness.

Arthus was writing in 1921, but matters are not so different today. We have reached a point in the multiplicity of scientific journals and publications at which the mind rebels against total immersion even in the scientific literature of a special branch of medicine. How much of it conforms to the 1892 definition of scientific method, the hard and stony path of classifying facts and reasoning upon them, and the ultimate appeal to the reason and not to the imagination ? It is well enough perhaps that this should be the path, and doubtless there is still something to be mined from fossicking the old workings of the hæmodynamics of the mitral valve, the hypotensive drugs, and the pharmacological action of digitalis from which such riches have come in the past ; but the creative scientist is already at work in fresh fields and pastures new.

CLIVE FITTS.

PHYSICIANS, PSYCHIATRISTS AND GENERAL PRACTITIONERS[1, 3]

DAVID C. MADDISON[2]
From the Department of Psychiatry, University of Sydney

BECAUSE of the difficulties in defining the term neurosis and, more importantly, because of the varying degree of reluctance shown by doctors in making a positive diagnosis of neurotic illness, it is difficult to obtain any reliable figure for the incidence of psychological disorders in the general practice of medicine. Estimates have ranged from 5% to 70% (Paulett, 1956) with a mean figure in the vicinity of 30% (Watts *et alii*, 1958). As yet no single body has concerned itself with the provision of diagnostic and therapeutic services in any way adequate to meet the needs of this extremely sizeable group. Psychiatrists by and large are governed by the power fantasy that psychological investigation and treatment should be carried out only by psychiatrists themselves; general physicians as a group see the problems as subsidiary in importance to those of the organic diseases, even the minor ones; neither of these two specialist bodies, and university educators least of all, seems to think it to be of the slightest importance to prepare general practitioners to handle this large segment of their case material. Various rationalizations are advanced for this neglect, the most pernicious being the oft-repeated phrase "but of course, psychiatry after all is only applied common sense". Fortunately there are signs that at long last the general practitioners themselves are awakening to the need for more satisfactory training in this field; general practitioner organizations in many countries, realizing the total inadequacy of their undergraduate preparation, are seeking help through post-graduate training programmes. Such a programme was organized in 1959 by the Post-Graduate Committee in Medicine in the University of Sydney; it was my very great privilege to lead the training group which formed the substance of this programme, and it is with the impressions and opinions derived from this experience that this present paper deals.

This is not the place for a theoretical discourse on the relative merits of the various types of training in psychological medicine. Suffice it to say that there is a very general impression that the usual didactic programme, adequate though it may be in many other areas of medical education, falls down very largely or completely in this particular sphere because of the inevitable involvement of the doctor's own personality in this type of work—an involvement which he cannot be helped to understand through the medium of lecture or text-book. No one interested in this field could fail to pay tribute to the pioneer work of Michael Balint, who has delineated the tasks of training very clearly in a series of papers (Balint, 1954, 1957*a*, 1957*b*), and who has published a summary of his experience in book form (Balint, 1957*c*), the latter being a volume which I believe should be required reading for every medical practitioner. The type of programme described in this paper is derived directly from Balint's work; a group of some eight to twelve general practitioners (or, for that matter, consultants) meet regularly for one and a half hours or more each week, the sessions being taken up by case reports of problem patients from the participants' own practices. These reports form the focus of free discussion amongst all members, with the psychiatrist leader attempting to clarify and interpret the various issues raised. The imparting of academic information by the leader is minimal, the emphasis throughout being on the nature of the doctor-patient relationship and the feelings aroused in both doctor and patient by the diagnostic and therapeutic transactions. Balint's own groups meet for periods of two years or even more; our own local group, much more in the nature of a pilot study, comprised nine selected general practitioners plus a psychiatrist-observer, a secretary and myself, and met on only 25 occasions. Even in this period, limited though it was in terms of time, very many vital topics were discussed. Neither the general practitioners nor myself, however, have any delusion that such a brief course was in any way adequate to produce in the participants what Balint has described as the "considerable though limited change in personality" which is the ultimate goal of this type of training programme.

[1] Received on November 24, 1960.
[2] Senior Lecturer.
[3] Delivered at the ordinary meeting of The Royal Australasian College of Physicians in Sydney on October 14, 1960.

In view of the fact that these doctors were so personally interested in obtaining a deeper understanding of psychological medicine that they were prepared to give up 25 consecutive Wednesday nights (and pay for the privilege of so doing), it may at first sight seem remarkable that one of the major difficulties encountered lay in their periodic reluctance to recognize psychogenic illness and, in particular, their reluctance to become involved therapeutically with neurotic patients. This phenomenon is fairly strictly analogous with the problem posed by the neurotic patient himself, who may consult a psychiatrist with a very strong motivation for personal help, but who is yet reluctant to abandon the various character defences which he has unwittingly employed for many years against deeper anxieties and conflicts. In the training group it was quickly apparent that many doctors had unconscious defences of an essentially similar kind, maintained for roughly the same type of reason—namely, to protect themselves from anxiety. The possible sources of this anxiety are discussed later in this paper.

DEFENCES AGAINST THE RECOGNITION OF PSYCHOGENIC ILLNESS

The mere fact that a case was brought forward for discussion in this seminar indicated that, at one level, the doctor recognized the relevance of psychological factors; it was thus even more striking to note how frequently these factors were minimized or, whenever possible, totally disregarded as ætiological agents. Some of these defences, which are by no means confined to general practitioners, but which are manifested frequently by physicians and by not a few psychiatrists, are as follows.

1. It was at times convenient to overemphasize the contribution of the patient's environment to his disturbed functioning; in some instances it was thought hopefully that the patient's difficulties could be seen as an inevitable result of such environmental forces—" he couldn't help being sick, look at his wife ". In coming to this hasty and ill-informed conclusion, the doctor is, of course, able to minimize the extent of the patient's own intrapersonal psychopathology and thus save himself the trouble of doing anything about it.

2. When patients showed obvious areas of normal psychological functioning, these tended to be hailed cheerfully as evidence of the unlikelihood of serious neurotic disturbance—" there can't be much emotionally wrong with him, look at the job he holds down ". Such a defence is based on the comforting but unwarranted assumption that intelligence or successful life achievement in some areas is an adequate protection against the development of neurotic behaviour.

3. There was a tendency to see neurosis only in terms of its overt, florid manifestations, of either a somatic or a mental nature—for example, hypochondriasis, phobias, and so on. Certain character traits, which to the psychiatrist may provide just as much evidence of neuroticism (for example, extreme submissiveness, promiscuity, etc.) tended to be overlooked as evidence of emotional disturbance; this omission, of course, is particularly easy in the case of character traits which are not rare in the general population.

4. The group as a whole would have granted strong recognition to the principle that a doctor's role is a scientific and therapeutic one, and not that of a moralist or preacher; when the latter attitudes were expressed in the group, it could be readily seen that this was in response to some aspect of a patient's behaviour which in some way emotionally disconcerted his physician. Then the problem tended to be solved by the taking up of a quite judgemental attitude; the patient could be more comfortably diagnosed, not as " sick ", but as " bad ". It was striking that the very word " neurotic " itself at times could have this connotation; it has, of course, in certain hands become the most juicy swear word in the physician's language.

5. Even against the doctor's better intellectual judgement (and often in defiance of all his medical training), various reasons inherent in his own discomfort at times drove him to desperate lengths to seek a physical cause for his patients' symptoms, or even to act as if such a cause was definitely present, though it could not in any way be demonstrated. It was no surprise that vague, hopelessly imprecise physical diagnoses were at times used as labels for obvious neurotic states—for example, " vitamin deficiency ", " fibrositis ", and so on. It did not seem coincidental that such diagnoses arose most frequently in the presence of an overt or suspected sexual problem.

6. Even in the presence of clear psychological and environmental problems, the concept of an " endogenous " illness seemed at times useful in an effort to minimize the importance of these. It clearly seemed easier on some occasions to postulate some hypothetical, unknown biochemical or physiological change to explain human behaviour than to see illness in psychological terms.

7. It was often more comfortable to accept the patient's own concrete, material explanation

for his illness than to study his psychological development and complexes; patients are only too anxious to convince doctors that such is the case, and clearly in the group doctors were at times very ready to be convinced. One case reported in detail was that of a young woman with a permanent colostomy, on to which she rationalized all her social and romantic difficulties; this rationalization was grasped at eagerly by her physician, although simple history-taking showed very clearly that her life difficulties substantially antedated the development of her organic illness. Perhaps one of the most beguiling traps laid for doctors working in this field lies in the extent to which patients unwittingly will manipulate various personal or environmental factors, which have a special seduction in that they are external and "real", in an attempt to evade any deeper consideration of their more abstract psychological function.

8. The important problem of the fear of missing physical disease was frequently raised in various forms. It was clear that relatively few doctors are as yet fully alive to the incalculable harm which can be done to patients by a misdiagnosis of physical illness when only a neurotic disturbance is present; and, conversely, that doctors are much too sensitized to the dire results of missing, even for a brief period, some physical abnormality of a fairly minor kind. There are various angles to this—the fear (almost wholly irrational in the vast majority of cases) that the patient may die; more importantly, fear of criticism from colleagues if organic disease is missed—a criticism which will be entirely lacking if the presence of neurosis is overlooked. Much more importantly still, the group came to realize that it was more comfortable to be able to diagnose organic than psychological disturbance. This aspect of "comfort" had several components. Certainly medical education as we know it fits the doctor much more adequately to treat organic disease; but more basically it was apparent that both patient and doctor felt more at ease within the framework of an organic, tangible diagnosis, and that this was, if anything, an even more important factor in the doctor than in his patient, although the attitude was usually rationalized as being entirely attributable to the latter.

DEFENCES AGAINST THERAPEUTIC INVOLVEMENT

When some of the above-mentioned defences had been worked through, the doctor was then left with a patient showing clear evidence of an entirely or largely psychogenic illness; the patient, of course, had not changed, only the doctor's view of him had altered. But at this point numerous resistances may be thrown up in an effort to avoid any active therapeutic contact—this again, it must be remembered, in a group of doctors who said they were anxious to attempt psychotherapy with their patients. There were again certain standard defences.

1. Patients tended to be rejected as therapeutic possibilities unless their own motivation was extremely high. A motivation involving a desire for personal change is, of course, of extreme importance in a patient about to undergo psychotherapy; but many patients will erect various superficial defences over a basic quite intense desire for help. Obvious indirect pleas for assistance often went unrecognized by the doctor, who felt contented if he "invited" the patient to contact him again if she felt the need to do so. This is a far cry from the occasional *furor therapeuticus* shown by the same doctor, who might involve his patient in an elaborate treatment régime aimed at removing physical symptoms which were barely inconveniencing him at all. Similar considerations governed the conception that "the patient is adjusted to her problem"; this statement may be true in some rare instances, but can clearly also be used as a justification for therapeutic inactivity.

2. It was clearly convenient at times to see certain patients as hopeless therapeutic prospects by reason of certain hypothetical deficits in their personalities. Such terms as "personality defect", "inadequate personality", "constitutional" and "congenital" were used in this connexion. It would certainly be unusual for physical deficits to be used as an excuse for the total avoidance of therapy.

3. There was a real fear of the effect of uncovering strong emotions in patients taken into psychotherapy; discussion of psychological problems was seen as likely to uncover turbulent aggression or chaotic sexuality, or to interfere with the happiness of the patient or his relatives. Here again there is some kernel of truth, in that psychotherapy, like any other valid medical treatment, may involve certain risks to the patient's balance. However, it was clearly defensive in some instances to see psychotherapy as an aggressive act, and on more than one occasion the idea was ventilated that it would be tantamount to "tearing down the patient's defences".

4. As was readily anticipated, the group reminded themselves and their group leader in virtually every session of the difficulty which the general practitioner has in providing

sufficient time for psychological treatment. There can be no doubt that this is a real problem; but it was also apparent in several cases that the avoidance of psychotherapy had itself led to many hours wasted in fruitless physical investigation and treatment. One doctor, who claimed that he had no time available to treat a certain patient with functional respiratory difficulties, later worked out that this patient had consulted him no less than 60 times in the previous twelve months.

5. No one can doubt that the present-day general practitioner receives a grossly inadequate basic training for work in this field. This lack was repeatedly stressed and sympathetically received; but it was also clear that this reality factor was at times also a convenient defence, and that, in other areas of medicine, doctors did quite frequently embark on treatment procedures for which they were also insufficiently prepared.

6. Resort to physical rather than psychological treatment was always available when the doctor was hard pressed; he might claim to be hard pressed in terms of time, but much more frequently he was really being hard pressed emotionally. Perhaps one of the greatest single gains to many group members was the realization that many of their physical therapies were illogical and irrational, growing out of an urgent desire to do something, to carry out some magical gesture in an attempt to get out of the rut into which the treatment situation had fallen. In this connexion a good deal of time was spent in the discussion of placebo therapy; no attempt was made to deny the possibility of a place for placebos in medical practice, but such treatment could also be used to avoid more personally involving treatment based on psychological principles. What might be called "placebo investigations" can be looked at in much the same way.

The Relationship between General Practitioners and their Consultants

Many of the cases discussed in the seminar had been referred at one time or another to consultants, often to several consultants in different medical specialties, on occasions to more than one consultant in the same specialty. The reasons for such referral were examined from time to time; some of them were logical, others seemed pretty clearly to be of a quite "magical" kind. Not infrequently referral to a specialist was used, consciously or unconsciously, as yet another defence against any personal emotional involvement with the patient by the general practitioner; at times also referral was employed unconsciously as a latent threat to the patient. Often cases were referred to a consultant physician as a final exclusion technique against organic illness; presumably there always remained the possibility that the physician in his brilliance would make sense out of the patient's symptoms where the general practitioner failed, or even the more beautiful thought that he would find a test which the general practitioner had not thought of carrying out (though this was often highly unlikely). Nevertheless, in very many instances it seemed quite illogical to assume that the physician in one brief interview would be able to obtain anything like as clear a picture as the local doctor himself had built up over a long period of previous contact with the patient, his relatives and his social situation. Referral to a psychiatrist often had even more complicated motives; in particular there was the recurring fantasy that psychiatrists had some secret ability to induce patients to talk about "new material".

Virtually always in these neurotic cases, the passage of the patient through the consultant's hands added little or nothing and in some instances detracted a great deal from the total situation. Often there was a distinct feeling of being "let down" if the case were not completely taken over by the consultant; in some of these instances the general practitioner clearly felt a strong need to sever completely all contact with the patient. Often the introduction of a consultant only confused the issue of who was going to care for the patient and be responsible for her; Balint has described this as the "dilution of responsibility", a common but relatively little recognized problem in medical care. It is sad to relate that, when the consultant physician confirmed the absence of any organic disease, his advice to the general practitioner was often unhelpful; the fine-sounding instructions to give "firm reassurance, superficial psychotherapy and sedation" came up so often that it became something of a catch-phrase among group members. The sadness lay in the realization that in the majority of instances the specialist physician, as much as the referring practitioner, had no real knowledge of how to proceed past this point.

The Personal Involvement of the Doctor

Just how much the doctor was going to become involved with his patient (or, conversely, how much he could avoid it) became more and more of a problem as the seminar proceeded, and, in

one very real sense, all the problems previously described were subservient to this major theme. In many instances it was seen by the individual doctors concerned that various aspects of their own personalities were by far the most important barriers against an adequate understanding and treatment of their patients. In some instances they reported irritation at various character attitudes and modes of behaviour of their patients — in particular flirtatiousness, apparent stupidity, hostility and ungratefulness tended to drive them back into a non-therapeutic position. Some members of the seminar were obviously concerned, at times almost disgusted, by patients who directly or in minimal disguise sought affection. In other instances the doctor's own personal views on life intruded into the diagnostic and therapeutic situation with quite serious results; if certain character attitudes shown by the patient were inimical to the doctor's own personality, he could too easily ignore the significance of them in the patient's neurosis. Problems of this type arose, for example, in connexion with an adulterous woman, with a young man who showed hostility towards his parents, and with yet another patient who behaved in a quite erotic way towards her practitioner.

Not surprisingly, the sexual question was the biggest difficulty of all. Though the embarrassment concerning sexual topics was often for convenience projected on to the patient, clearly all too often it arose primarily in the doctor himself; at least two doctors felt that to take a history of patients' sexual function might lead to their being labelled as "dirty old men" in their practices. Certainly the doctor's personal comfort was not necessarily in the patient's best interests; at times, to maintain his own peace of mind, he found that he had had to ignore an extremely relevant sexual problem.

In general it was apparent that an awareness of the doctor's own response to his patients' problems was essential if he was to move therapeutically in a logical and rational way. But an awareness of an emotional relationship between doctor and patient implied to many the very real threat of some degree of emotional closeness, and the members of the seminar were seen to vary very greatly in their capacity to tolerate, and perhaps even encourage, a close relationship with their patients. On the one hand, there was the doctor who could see no real difference between his patients and his friends, at the other extreme the doctor who felt that the successful doctor-patient relationship should be "depersonalized"; in this view the doctor should at all times be "detached" emotionally from his patients, and should react as a "technician", though in a social rather than a physiological situation. The conclusion is inescapable that the type of relationship developed is irrevocably connected with the doctor's own personality and his own needs in medical practice; for this reason the group saw that there could be no rule as to the "best" type of relationship, and that each doctor must inevitably find this out for himself on his own terms. A special difficulty centred round the question of dependence; once again, the amount of dependence permitted varied over a wide range. Involvement in psychotherapy was seen by some to be dangerous on this account; it was acceptable that doctors might have to act as a crutch for some neurotic patients, but there was an exaggerated fear that dependence might pose serious dangers for both doctor and patient. One or two of the members who most feared highly dependent patients were those who constantly made decisions for their patients, thereby clearly aggravating the latter's tendency to lean on them. Very obviously the situation became very difficult when the emotional involvement between doctor and patient was too intense; the opinion was expressed that if the doctor became "too involved" the situation tended to get "out of control". Frequent and approving reference was made to Balint's phrase "prescribing the doctor's personality"—in other words, that in giving adequate psychological support something was required of the doctor's own psychological make-up, but that this something could not easily be prescribed in a foreseeable or accurate dosage.

CONCLUSIONS

This teaching project had no more elaborate aims than that of a pilot study; it was hoped to explore the difficulties of psychological diagnosis and treatment as they confront the general physician and general practitioner. That such an exploration is necessary seems abundantly clear. Whether or not the amount of stress disorder is increasing in the community, there is already far too much in existence for it to be handled even by a vastly increased number of psychiatrists, even if patients were more ready than they are at present to put their problems into psychiatric hands. In our current preoccupation with cellular biochemistry and chromosomes, it is easy—because it is comfortable—to forget that, however holistic one may be in one's approach to man, the vast area of personal suffering and community distress caused by psychiatric illness can in only a small number of instances be explained in the

language of the so-called basic sciences; nor is it likely in our lifetime that much more will be achieved in this way. We have therefore no choice other than to face up to the years of neglect which have left the general practitioner and the physician in monumental ignorance of such a substantial segment of medicine, and must attempt, at both an undergraduate and a post-graduate level, to provide adequate programmes to teach a rational management of those disorders due to psychological conflict.

I can do no better in conclusion than quote from a letter written to me after the termination of this seminar by one of the participating practitioners; to my mind the necessity for the involvement of the general practitioner in this problem has never been set out more succinctly. He writes:

> . . . the problem of neurotic illness has been left on the general practitioner's door-step. To this the purist may object; one might as well deplore the weather, for the situation is there, to be coped with. And the G.P. has some ready made tools. Mostly he holds the powerful weapon of emotional contact. Also he is the practical expert on human ecology. He has a permit to move through the structure of the social system. He deals not with a segment of the body, as do most specialists, or with a segment of the life of that body, as do most hospital doctors, but with the whole man-plant in its native soil.

ACKNOWLEDGEMENTS

I am indebted in the preparation of this paper to all the members of the training group, not only for their ready participation in what was at times a very stressful situation, but also for the complete freedom with which they have permitted me to report our discussions. The quotation which concludes this paper is from a letter written by Dr. P. P. Manzie.

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METABOLIC STUDIES IN STARVATION[1, 2]

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SUMMARY

Three obese females were studied during starvation (0 to 500 Calories per day) and light activity for 18, 28 and 34 days, during which they were given vitamins and liberal amounts of water, and two of them were given electrolytes. Studies were then continued on two subjects given 500 Calorie diets with contained protein.

They experienced little or no hunger, and no untoward effects except halitosis, slight ketonuria and sensitivity to cold. Weight loss amounted to 9·3, 14·1 and 9·5 kg., averaging 810, 330, 250 and 250 grammes per day in successive weeks. This was analysed in terms of its components by the methods usually used in metabolic studies and indirect calorimetry.

Protein catabolism declined as starvation proceeded to a minimum level of 12 to 25 grammes per day. It was decreased by norethandrolone and by carbohydrate feeding. The average daily losses of protein during succeeding weeks were 55, 36, 28 and 18 grammes. Overall, protein accounted for 7·6% to 9·1% of the weight loss and provided 5·0% to 6·9% of the caloric expenditure. Protein lost during starvation ranged from 704 to 1156 grammes, which represent 2·8 to 4·6 kg. of muscle and other cellular tissues. Creatinine excretion gradually fell; it accounted for about 5% of the nitrogen loss initially and 15% in the later stages.

Carbohydrate losses were estimated at 495 to 1050 grammes, accounting for 3·5% to 11·0% of the weight loss and for 3·0% to 6·4% of the Calories. Fat losses amounted to 4·1 to 6·5 kg., being 44% to 68% of the weight loss and providing 87% to 90% of Calories. The average daily loss of fat was 215 grammes. The gaseous exchanges and respiratory quotient fell, and the basal metabolic rate fell more steeply than the body weight or surface area.

Water balance was estimated from measurements and calculations made in two slightly different ways, and the total body water was measured in one subject. All items of losses and gains were determined daily, including metabolic water and evaporation. The cumulative net losses of water reached a peak of 6·2 litres in one subject and were 3·8, 6·0 and 1·2 litres at the end of starvation in the three subjects. The final " corrected " water balances, when allowance was made for the discharge of cell water associated with protein catabolism and for possible initial imbalances, were −1·6, −1·1 and +0·5 litres.

Serum electrolyte levels showed only minor changes. Potassium, sodium and chloride were apparently retained in store in the two subjects who were given these electrolytes. There was a net loss of potassium in all subjects, but in two the potassium balance was normal when account was taken of electrolytes released from cellular breakdown.

Observations from this study and from the literature have been interpreted as emphasizing the idea that (*a*) negative nitrogen balance means the amputation of cells so that cellular water and electrolytes are released in proportion to the protein catabolized, and (*b*) the " desirable " or normal water balance recognizes a constant volume of extracellular fluid plus an intracellular volume which is proportionate to the cellular protein mass. This concept, the nature of obesity tissue, nitrogen metabolism and the possible importance of essential amino acids and of creatinine metabolism are discussed.

MENTION of starvation usually brings to mind pictures and stories of emaciated bodies in tattered rags, lost explorers, wars, fasting-for-a-cause and the like. Thoughts range far afield to other places and other times, while less spectacular examples, not uncommon in clinical practice, attract scant attention and frequently pass unrecognized. In some instances starvation, partial or complete, is deliberately prescribed as treatment for obesity; in others it is tacitly accepted as a natural concomitant of a wasting illness, or as an inevitable but recognized hazard in the management of some condition such as œsophageal stricture. However, sometimes starvation may proceed unheeded, for short or long periods,

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particularly in post-operative conditions and in comatose or very ill patients. Our own interest in the subject was aroused by the plight of patients suffering from acute oliguric renal failure, who can rarely consume adequate amounts of food because of the nature of their illness and the restrictions placed on their dietary intake. An additional hazard in these patients is the accumulation within the body of the end-products of metabolism, because of their failure to excrete urine. It would seem to be important, therefore, particularly for the intelligent treatment of anuric patients, but also for the better understanding of all clinical conditions in which partial or complete starvation occurs, that the metabolic processes concerned should be clearly understood, and that methods of combating some of the more offensive aspects should be found.

Starvation has, of course, been studied previously, particularly in the latter part of the nineteenth century and in the early twentieth century. The subjects usually were professional fasters, and the investigations were chiefly concerned with gross weight loss and the urinary loss of nitrogen. The first really detailed studies were made by Benedict (1915), and his investigation of 31 days of fasting by Levanzin is a remarkably comprehensive metabolic study which in many respects has not since been equalled. Subsequent studies have been concerned more with partial starvation than with complete starvation, and for the most part have concentrated on some particular aspect, such as nitrogen metabolism or electrolyte balance. The whole subject was exhaustively reviewed by Keys and his colleagues (1950) in their published account of the Minnesota experiment, in which the effects of prolonged undernutrition and subsequent rehabilitation were studied in a number of volunteers. Moore (1959), whose own metabolic studies have contributed a great deal in this field, particularly in relation to the post-operative state, has given one of the best recent descriptions of starvation.

The most obvious feature of starvation is loss of body weight, which is most rapid during the first week or so. The loss of weight is made up of losses of all elements of the body tissues—glycogen, fat, protein, minerals and water. Glycogen is lost during the first few days; fat is lost continuously and supplies the bulk of the caloric needs; while the loss of protein occurs initially at the same rate as before starvation and then usually declines. The mineral loss is variable and contributes little to the overall change in weight, though it has some influence on the behaviour of water. The loss of water is inevitable, but variable; whether the actual losses sustained are interpreted as being normal or abnormal depends on the observer's concept of " water balance ".

Oxygen consumption steadily declines during starvation, out of proportion to the more modest decrease in body weight, surface area and other parameters. Carbon dioxide production also decreases, and the respiratory quotient rapidly falls to about 0·73, indicating exhaustion of available body carbohydrate and conversion to a metabolic fuel which is predominantly fat. Ketosis appears within a few days, but is not usually severe. The excretion of urea decreases, and this largely accounts for the overall decline in nitrogen loss. Uric acid excretion is variable, urinary ammonia excretion increases, and creatinine excretion progressively falls. Creatine excretion may increase.

All in all, the published observations show that complete starvation is tolerated surprisingly well for periods of 30 days or so. Hunger usually disappears, in contrast to what is experienced when the caloric needs are only partially unsatisfied, and weakness, giddiness and other disabilities are minimal or absent. Consequently, complete and repeated fasting has been advocated as a simple and safe treatment for the reduction of obesity (Folin and Denis, 1915). Nevertheless, heavy physical exercise is inadvisable during fasting and has been shown to be deleterious (Taylor *et alii*, 1954), and obviously the period for which starvation can be innocuously endured is limited. The longest recorded fast is that of Terence McSwinney (Sunderman, 1947), who fasted for 74 days till his death.

The relevance of a study of starvation to problems concerned with the management of acute renal failure will be elaborated elsewhere; but the principle items of interest relate to nitrogen, potassium and water metabolism, particulary in the early phase of starvation. Many of the published studies do not deal in detail with these aspects, and it was largely because of this that the present study was undertaken. The results illustrate many of the important features of drastic starvation, carried on for as long as 29 days, and lead to the concept of " cell release " being emphasized. Cell release implies the discharge of water and electrolytes from cells in proportion to the amount of cellular protein catabolized. It is an important item which is often neglected when water metabolism and potassium balance are being considered.

SUBJECTS AND METHODS

Subjects

Three young, healthy, unmarried females, who were grossly overweight and obviously obese, were admitted to hospital for weight reduction, and volunteered to act as subjects for these investigations. Subject A was aged 20 years, 159 cm. in height and 116·7 kg. in weight, which is 212% of the standard weight for that age and height. The corresponding data for the other subjects were: Subject B, 18 years, 179 cm., 119·8 kg., 176%; Subject C, 17 years, 167 cm., 107·4 kg., 185%. Both A and C seemed to be well balanced psychologically, but subject B gave evidence of being quite unstable at times. Procedures were carefully explained and the necessity for cooperation and honesty was stressed.

Treatment

The subjects were allowed to be ambulatory, but were confined to the general research ward and restricted to light exertion. Supervision was regular and frequent, but not continuous. After their admission to hospital, there was a control period of a few days, followed by the experimental period, lasting 23 to 39 days, and characterized by complete, or almost complete, caloric starvation, the ingestion of liberal amounts of water, the administration of vitamins, the provision of additional electrolytes to two subjects' short periods of treatment with norethandrolone ("Nilevar") and, finally, the provision of 500 Calorie diets with or without contained protein. The exact treatment schedule varied for each subject, as is shown in Table I and in the subsequent discussions. The various juices and electrolyte solutions were made up in bulk and stored, and then dispensed, as also was the drinking water, from weighed containers. The oral intake was ingested as evenly as possible throughout the day, commencing after the morning tests and ending not later than 9 p.m. Norethandrolone was given orally, in doses of 10 mg. every six hours, for periods of three to five days, as shown in the later figures. Subjects were not allowed to ingest any other drugs, fluids or food.

Observations

Body weight was measured at the same time each morning on a beam-type balance accurate to ±20 grammes, with the subject clad in a standard gown, and after the bladder had been emptied.

Urine was collected by the patient. Immediately after having been passed into a stainless steel container, the urine was poured into a large flask containing a known amount of 6N sulphuric acid solution as preservative, and kept stoppered. The 24-hour collections were weighed and the volume was measured. Specific gravity was measured with a hydrometer as an independent check on the estimate derived from the weight and volume. The urine was analysed for its content of total nitrogen, sodium, potassium, chloride, creatine, creatinine and total solids. A qualitative test for ketones was performed by the use of the nitroprusside reaction in tablet form.

Fæces were weighed and homogenized with water, and an aliquot was dried to determine the water content. The contents of nitrogen and electrolytes were measured, but not used in the final calculations, because it was assumed that they were derived from the pre-starvation period; even had they been included, the effect on the results would have been negligible because of the small amounts involved.

Blood was withdrawn at intervals for routine hæmatological examinations and for the determination of hæmatocrit, plasma proteins, contents of sodium, potassium, chloride, bicarbonate, non-protein nitrogen and creatinine, and indices of liver function. The amounts of blood removed were recorded, and appropriate allowances were made in the calculations for the loss of weight, water and nitrogen.

TABLE I

Subject	Duration (Days)	Diet	Calories per Day	Sodium (mEq)	Potassium (mEq)	Chloride (mEq)	Carbohydrate (Grammes)	Nitrogen (Grammes)	Fat (Grammes)
A	18	Tap water Orange juice 100 grammes Vitamins	50	Negligible	4	Negligible	13	0·1	—
	5	Low-calorie protein-containing	500	Unknown	Unknown	Unknown	Approximately 40	6·5	Approximately 20
B	10	Distilled water Tomato juice 500 grammes Added electrolytes Vitamins	100	127	35	143	25	0·65	—
	18	Distilled water Electrolyte solution	0	140	41	180	—	—	—
C	29	Distilled water Tomato juice 500 grammes Added electrolytes Vitamins	100	129	38	142	25	0·50	Negligible
	5	Tomato juice Pineapple juice Added electrolytes Distilled water Vitamins	500	132	54	149	125	0·89	Negligible
	5	Tomato juice Milk Distilled water Vitamins Added electrolytes	500	143	60	154	50	3·40	Approximately 25

Menstrual losses were measured in the following way. Weighed absorbent pads were supplied; they were changed frequently, the used pads were kept in an airtight weighed tin, and the extra weight was assumed to be made up solely of whole blood. The total losses on each occasion were less than 70 grammes for the five to seven day periods. Appropriate allowances were again made in our calculations.

Losses from the skin of sodium, potassium, chloride and nitrogen were measured in Subject B towards the end of the starvation period. After a thorough shower followed by a bath in distilled water, the subject wore an electrolyte-free garment covering the entire body except the head, neck and hands for 24 hours. At the end of that time the covered areas were swabbed down with distilled water, the garment was soaked in these washings for 24 hours, and aliquots were then analysed. Subsequent experience with this method has shown that it yields reproducible results.

Total body water was measured by the antipyrine technique immediately before starvation and at the mid-period, and again at the completion of the test period of starvation in Subject C. Attempts to measure the total body water and other spaces in Subject B were unsuccessful because of difficulty in venepuncture.

Respiratory exchanges were measured at frequent intervals by the Douglas bag technique and analysis of gas in the Haldane apparatus, giving estimates of the basal oxygen consumption, the carbon dioxide production and the respiratory quotient. More prolonged measurements, over periods of one to two hours, were made with a Wolff Integrating Motor Pneumotachograph (Wolff, 1958), with the subject in the basal state, and also during periods of typical activity round the ward.

Biochemical Methods

The methods used were as follows. Total nitrogen and non-protein nitrogen was measured by an adaptation of the micro-Kjeldahl technique of Mackenzie and Wallace (1954); creatinine was measured by the Fuller's earth method of Edwards and Whyte (1958); antipyrine was estimated by Edwards' method (1959); chloride was estimated by the method of Schales and Schales (1941); bicarbonate was estimated by the usual Van Slyke method; sodium and potassium were estimated by flame photometry, multiple standards being used. The electrolyte content of tomato juice was determined after preliminary ashing at 400° C. Creatine in urine was estimated by difference after converting creatine to creatinine and measuring the total creatinine content; the possible error is large, especially when the ratio of creatine to creatinine is small. Attempts to absorb creatinine without creatine on to Fuller's earth (Benedict *et alii*, 1955) were not successful. Urinary water and solids were measured by weight, aliquots being evaporated at a low temperature. While not a very satisfactory procedure, this yielded results consistent with the sum of measured solids of urea, creatinine and electrolytes. A similar method was used to measure the water content of fæces and of the tomato juice.

Other measurements were made in the routine laboratory services of the hospital.

Assumptions and Calculations

Nitrogen Metabolism.—The net daily loss of nitrogen from the body was calculated from the sum of the losses in urine, in blood and from the skin, an allowance being made for any oral intake. The cutaneous loss was assumed to be 50 mg. per day (based on the measured loss in Subject B). The net loss of nitrogen from the body would be the same as the loss of nitrogen from cellular protein only if no changes had occurred in the pools of plasma proteins and non-protein nitrogen. Therefore, in order to estimate the cellular nitrogen balance, an appropriate adjustment was made, usually small, based on the plasma protein and non-protein nitrogen levels and the estimated changes in plasma volume (from the hæmatocrit) and total body water (from the water balance). The cellular nitrogen loss was multiplied by 6·25 to represent the amount of protein catabolized, which assumes that nitrogen forms a constant proportion of the protein from which it is derived at all levels of protein turnover. The cellular protein has been assumed to come from cellular tissue with an average composition of 20 grammes of solids (mostly protein) and 80 grammes of water per 100 grammes of whole tissue (*Documenta Geigy*, 1956). As about 20 grammes of this water is believed to be in the extracellular phase, it can be assumed that there are 20 grammes of protein (that is, 3·2 grammes of nitrogen) in every 80 grammes of cells.

Energy Expenditure.—The total daily expenditure of energy can be regarded as being a basal level throughout the 24 hours plus an amount required for activity. The basal levels in our subjects were estimated from (*a*) the protein destruction as calculated from the measured daily nitrogen losses, and (*b*) the carbohydrate and fat catabolism as calculated from the basal gaseous exchanges by the methods of indirect calorimetry using the relationships shown in Table II.

TABLE II

In Metabolizing One Gramme of	Oxygen Absorbed (Litres)	Carbon Dioxide Eliminated (Litres)	Calories Provided	Metabolic Water Produced (Grammes)
Protein ..	0·9963	0·7739	4·1	0·41
Carbohydrate	0·8288	0·8288	4·1	0·60
Fat ..	2·0193	1·4273	9·3	1·06

Based on these principles, working equations were derived for estimating the amounts, in grammes, of carbohydrate (C) and fat (F) involved in the non-protein gaseous exchanges:

Non-protein O_2 consumption
($N.P.O_2$, l. per day) $=0·8288C+2·0193F$
Non-protein CO_2 production
($N.P.CO_2$, l. per day) $=0·8288C+1·4273F$
Thus, F (grammes) $=\frac{N.PO_2-N.P.CO_2}{0·5920}$
and C (grammes) $=4·1156\ N.P.CO_2-2·9090\ N.P.O_2$.

No allowance was made for the incomplete combustion of fat resulting in the production of ketosis. Incomplete fat combustion gives a respiratory quotient which is lower than when fat is completely burnt. The effect of this in our method of calculation is to over-estimate the amount of fat burnt and to under-estimate the amount of carbohydrate involved, and, in fact, negative values for carbohydrate consumption were sometimes obtained (and omitted from subsequent calculations).

The additional daily allowance made for energy expended in activity, over and above the basal state, varied slightly in the three subjects, but was about

450 Calories. In each case the figure was determined by reference to the diary in which each subject recorded the times spent in performing various tasks and from measurements of the respiratory exchange recorded during periods of typical activity. Variation from the accepted figures is unlikely to be gross, and would not substantially affect the overall results. The energy required for non-basal activities was assumed to be derived solely from fat (45 to 50 grammes per day). This seems reasonable, especially in the later stages of starvation, when protein catabolism contributes little to the daily energy balance and the labile glycogen stores are severely depleted.

Water Metabolism.—Changes in the weight of water within the body were calculated daily from the difference between gains and losses. Water was gained from oral intake, from injections (antipyrine solution in Subject C) and from metabolism. Water was lost from the body in urine, in fæces, in blood (menstruation and blood samples) and by evaporation. Metabolic water was calculated from the amounts of protein, carbohydrate and fat burnt each day, by the use of the figures given in Table II. The daily evaporative loss was obtained from the change in total body weight from day to day, after all other items of weight gain or loss had been taken into account, including the weights of oxygen absorbed and carbon dioxide eliminated. The water content of ingested fluids, injected solutions, urine, fæces and blood was mostly measured by evaporating samples to dryness as described earlier.

Except for the total body water in Subject C, water spaces and compartments were not measured in these subjects. Measurement of the hæmatocrit and serum electrolytes were examined for any suggestion of changes in the volumes of plasma and extracellular fluid. Changes in the fluid volume considered to be desirable for a body whose cell mass was changing were also calculated by making allowances in the overall water balance for the loss of water accompanying the destruction of cells; the loss of 1 gramme of cellular protein was assumed to be associated with the loss of 3 grammes of intracellular water. These changes in the desirable volume are referred to as the "corrected water balance".

Electrolyte Metabolism.—Daily balances were drawn up for sodium, potassium and chloride, the gains by ingestion and injection and the losses in the urine, in blood and from the skin being taken into account. Daily skin losses were assumed to be 4 mEq of sodium, 1 mEq of potassium and 4mEq of chloride. In calculating changes in the "desirable" electrolyte load, a further allowance was made for the discharge of intracellular electrolytes accompanying protein loss. It was assumed that the breakdown of 100 grammes of cells caused the loss from the cells of 10 mEq of potassium, 4 mEq of sodium and 3mEq of chloride. Changes in the "desirable" electrolyte load are referred to as the "corrected electrolyte balance".

RESULTS

Subjective Experiences and General Observations

These subjects were not at all apprehensive about their ability to starve, and they did not experience hunger at any stage. They had no real desire for food, but felt they could eat if tempted, and deliberately avoided the meal table for the first few days. All were euphoric in the initial stages of starvation and manifested increased physical activity that gradually waned as the experiment proceeded. None complained of lack of energy. Transient episodes of faintness occurred in two subjects in association with the assumption of the upright posture. Undue sensitivity to cold was apparent in the later stages of starvation, occurring mainly in the mornings even on mild days, so that one subject was reluctant to leave her bed because of difficulty in keeping warm. Halitosis became evident after two or three days, coinciding with the appearance of ketones in the urine, and persisted throughout the period of starvation. The breath was sweet and rancid, and was not improved by cleaning the mouth. Subjects noticed a furriness of the mouth, probably due to the excessive growth of papillæ in the absence of the mechanical effects of chewing solid food. At the conclusion of starvation all subjects had difficulty in eating all their diet of 500 Calories because of nausea and fullness; one subject said she would prefer to starve.

Menstruation occurred during the experimental period in two subjects, as a normal event, and also following the withdrawal of anabolic hormone. Fæces were not passed by one subject, and only small amounts were passed by the other two subjects on one or two occasions. The water intake was copious and maintained as constant as possible. No thirst was experienced; in fact, it was necessary to encourage the subjects to drink more water than they desired, so that natural fluctuations in water balance could occur without being hampered by a shortage of intake. Voluntary daily intakes during the first week would have been insufficient to provide for an adequate urine volume were a normal water balance to be maintained. The urinary output was variable despite constancy of fluid intake. A reasonable constancy of creatinine excretion supported the reliability of urine collections, so that the variations in urinary volume indicated variations in evaporative losses and/or changes in the bodily content of water. At times urine output fell to "oliguric" levels, less than 400 ml. per day, but the specific gravity was not above 1·025 and there was no nitrogen retention. Subject B actually became "anuric" one day, passing only 30 ml. This episode was apparently precipitated by voluntary abstinence from water for more than 24 hours and was promptly overcome by giving a water load. Ketones appeared in the urine after two or three days and persisted at a moderate level throughout starvation. A diet of 500 Calories, chiefly as carbohydrate, reduced the ketonuria, but did not eliminate it.

There was no obvious physical or mental disability in two subjects, but Subject B was always somewhat difficult and refractory and became more so as the experiment proceeded. The basal pulse rate and blood pressure fell as starvation progressed, the change being most

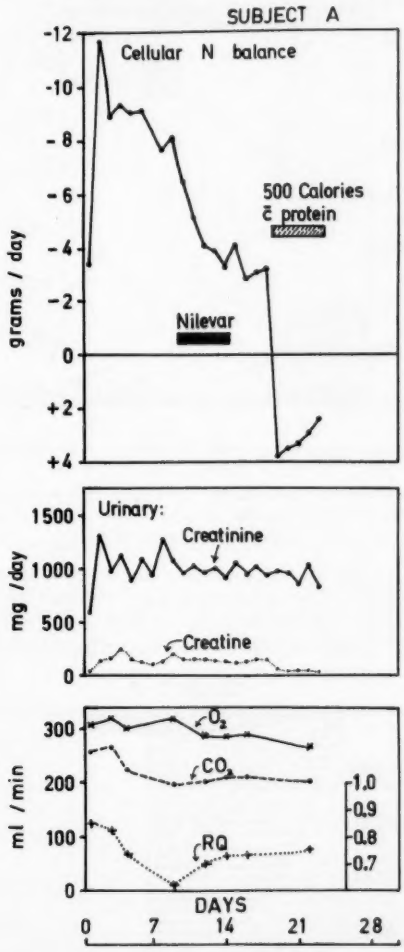

FIGURE I
The daily nitrogen balance and other results in Subject A

rapid in the first week. Gross appearance altered little during starvation. The most obvious changes were thinning about the face, wrists and abdomen.

Body Weight

Weight was lost rapidly at first, more slowly in the later stages, and during some periods weight was actually gained owing to water retention. Altogether, Subject A lost 9·30 kg. in 18 days, Subject B 14·12 kg. in 28 days, and Subject C 9·50 kg. in 34 days. The changes in weight of the three subjects are plotted in Figures V, VI and VII, and their average daily losses at different stages during starvation are

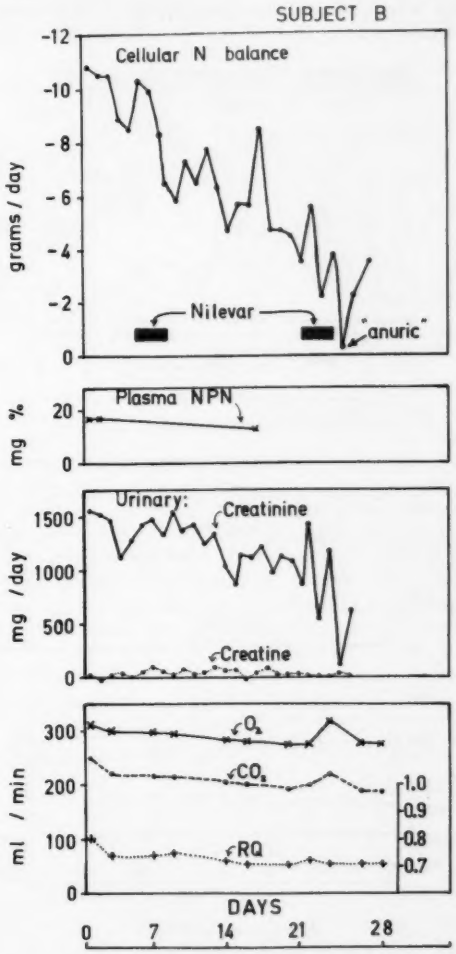

FIGURE II
Results in Subject B

given in Table III. The pattern was slightly different in the three subjects. On the average, 810 grammes were lost per day during the first week, 330 grammes per day in the second week, and about 250 grammes per day in the third and fourth weeks. The loss in weight must be due to the net loss of body protein, carbohydrate, fat, water and inorganic substances. The weight of the latter is presumed to be negligible.

Nitrogen

Apart from a temporary decrease on the first day in two subjects, the daily urinary loss of nitrogen continued at about the pre-starvation rate in the early part of starvation and then gradually declined. Since there was little or no intake of nitrogen in these subjects and losses by other routes were small, the urinary loss closely reflects the net loss of nitrogen from the

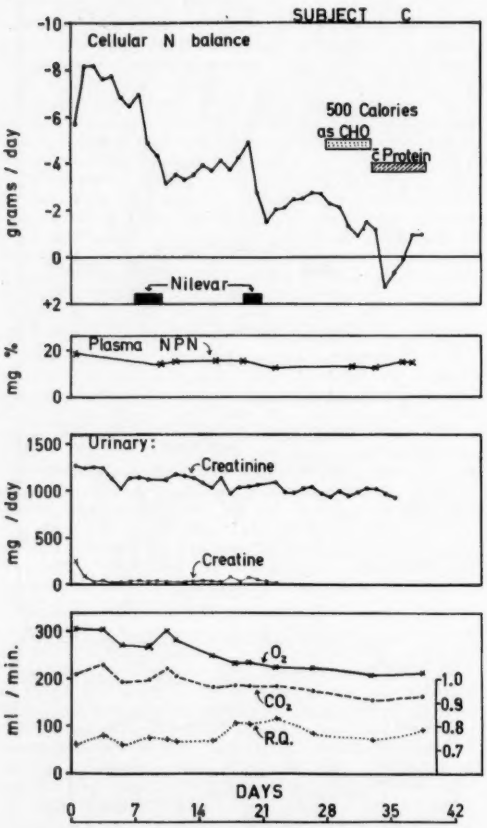

FIGURE III
Results in Subject C

body. However, when these adjustments were made and allowance was also made for changes in plasma proteins and in the nitrogen contained in the body water, the day-to-day cellular nitrogen balances were estimated for each subject and are shown in Figures I, II and III. The net losses fell to between 2 and 4 grammes of nitrogen per day (the equivalent of 12 to 25 grammes of protein) towards the end of the periods of starvation. The plasma level of non-protein nitrogen (N.P.N.) fell gradually.

The administration of norethandrolone for short periods caused a prompt decrease, sometimes preceded by a slight increase, in nitrogen

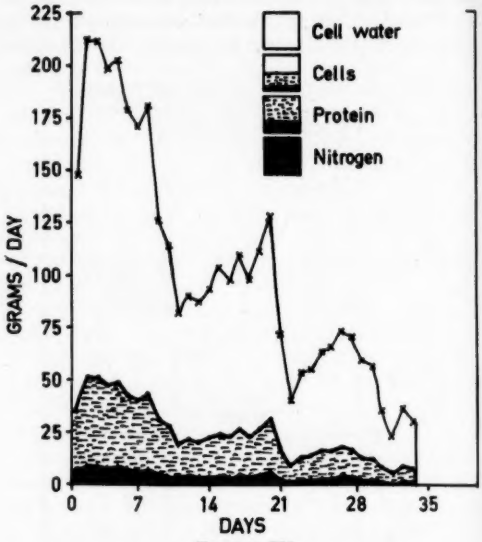

FIGURE IV
The weight of " cells ", and their contained protein and water, required each day to provide the observed losses of nitrogen in Subject C.

loss. This was observed to occur at both high and low levels of nitrogen loss. Withdrawal of the drug was followed by an increased nitrogen loss. These effects were somewhat obscured

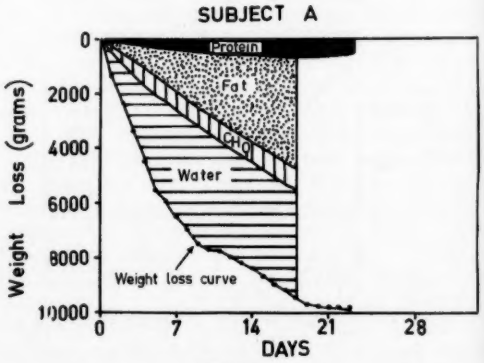

FIGURE V
The progressive loss of weight in Subject A, showing the cumulative contributions of protein, fat, carbohydrate and water

by the natural fluctuations in excretion and by the general decline induced by starvation, but are particularly well shown in Subject C (Figure III).

The subsequent addition of a carbohydrate diet for Subject C caused a steady decrease in nitrogen loss, while a protein-containing diet

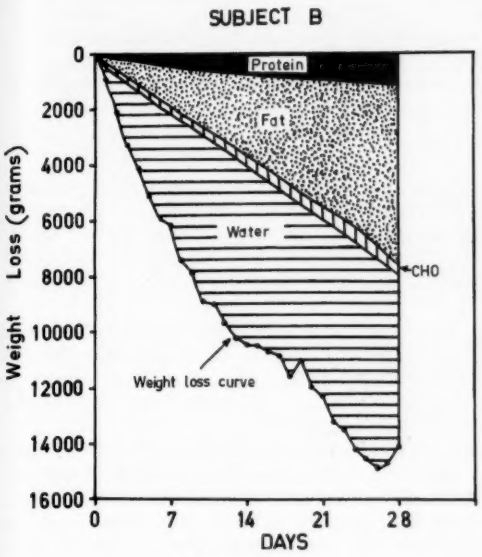

FIGURE VI
Composition of the weight loss in Subject B

caused a prompt reversal of the nitrogen balance in Subjects A and C. This latter effect was not sustained, and the balance again became negative in Subject C. The plasma N.P.N. level rose when protein was ingested.

The day-to-day creatinine excretion was reasonably steady in all subjects, except towards the end of the experimental period in Subject B, and decreased slowly as starvation proceeded. It accounted for only about 5% to 7% of the

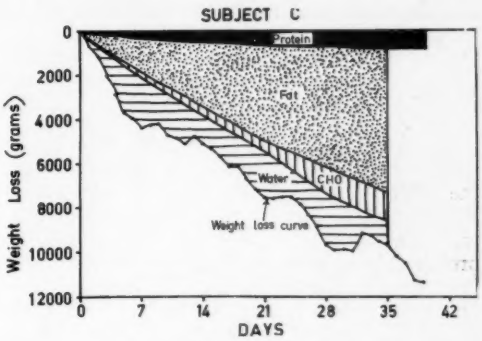

FIGURE VII
Composition of the weight loss in Subject C

nitrogen losses initially, but for 15% to 20% at the end of starvation. Creatine excretion showed no particular changes during starvation, and no evidence of being increased by androgenic hormones as has been described by Stokes *et alii* (1959). In Subject A, creatine excretion was maintained at about 150 mg. (as creatinine) per day, and then promptly dropped to about

TABLE III

Average Daily Losses (Grammes) of Body Weight, Protein, Carbohydrate, Fat and Water in the Three Subjects[1]

	Subject	Days 1 to 3	Days 4 to 7	Second Week	Third Week	Fourth Week	Fifth Week
Body weight ..	A	1133	775	271	275		
	B	1100	718	616	266	254	
	C	673	595	103	341	308	(28)
Protein	A	49	51	36	21		
	B	66	59	45	36	20	
	C	44	45	28	26	15	10
Carbohydrate ..	A	175	27	2	37		
	B	62	22	14	9	8	
	C	18	16	19	81	79	6
Fat	A	175	234	246	226		
	B	195	262	219	226	253	
	C	221	212	205	191	154	176
Water	A	734	463	(13)	(9)		
	B	777	375	338	(5)	(27)	
	C	390	322	(149)	43	60	(220)

[1] Any gains in weight are placed in parentheses. The figures for water are derived by subtraction of the other items from the loss of body weight.

TABLE IV

The Total Weight Loss and its Components

Subject	Duration of Starvation (Days)	Total Loss of Weight (Grammes)	Losses (Grammes) of Components			
			Protein	Carbohydrate	Fat	Water
A	18	9300	704	673	4086	3837
B	28	14,120	1156	495	6519	5950
C	34	9500	868	1050	6423	1158

50 mg. per day when the 500 Calorie protein-containing diet was taken.

The cellular nitrogen losses have been recalculated in terms of protein by assuming that the nitrogen lost at all stages of starvation represented 16% by weight of the protein which was catabolized to provide it. The amounts of protein broken down each day in Subject C are illustrated in Figure IV, and the average daily losses of protein in each of the three subjects at different stages during starvation are given in Table III. Overall, the average daily losses during successive weeks were 55, 36, 28 and 18 grammes. The progressive cumulative losses as starvation proceeded are shown in relation to the loss of weight and loss of other fuel substances in Figures V, VI and VII. By the end of the period of starvation Subject A had lost 704 grammes of protein in 18 days, Subject B 1156 grammes in 28 days, and Subject C 868 grammes in 34 days (Table IV). It is important to realize that these losses of protein were presumably derived from four times their weight of cellular material. The relative weights of nitrogen, protein and cells involved in the daily transactions in Subject C are shown in Figure IV to illustrate this point.

The calorific contribution from protein catabolism can be easily judged from Tables III and IV. There were minor individual differences. The average caloric contributions, as percentages of the total number of calories supplied from the body tissues, were 9·1, 6·5, 5·0, 3·4 and 2·4 in successive weeks. Overall, the protein loss accounted for 7·6% to 9·1% of the total loss of weight, and for 10·4% to 14·1% of the loss of weight excluding water, and provided 5·0% to 6·9% of the caloric needs.

Respiratory Exchanges

The basal oxygen consumption and carbon oxide production fell progressively during starvation. Carbon dioxide production initially fell more rapidly than the oxygen consumption as is indicated by the fall in respiratory quotient (R.Q.) during the first few days to a level of about 0·73, which was then maintained throughout starvation. These features are illustrated in Figures I, II and III. There was an unexplained rise in the R.Q. to about 0·8 in Subject C from about the seventeenth to the twenty-first day.

The reduction in oxygen consumption was proportionately greater than the reduction in body weight, surface area, creatinine excretion or lean body mass. This was most pronounced in Subject C and least so in Subject B; illustrative results for Subject C are given in Table V. Treatment with anabolic hormones had no noticeable effect on the respiratory exchanges, but the ingestion of food caused the R.Q. to rise, though the consumption of oxygen was practically unchanged.

TABLE V

Average Measurements at Different Times during Starvation in Subject C

The percentages refer to pre-starvation values

Days	Body Weight (Kilograms)	Surface Area (Square Metres)	Oxygen Consumption (Millilitres per Minute)	Creatinine Excretion (Milligrammes per Day)
1– 5	104·9 (99%)	2·117 (99%)	292 (97%)	1219 (101%)
6–10	102·0 (96%)	2·092 (98%)	274 (91%)	1103 (92%)
11–15	101·2 (95%)	2·085 (98%)	254 (84%)	1133 (94%)
16–20	100·1 (94%)	2·076 (97%)	236 (78%)	1038 (86%)
21–25	98·1 (92%)	2·059 (96%)	220 (73%)	1024 (85%)
26–30	97·2 (91%)	2·050 (96%)	217 (72%)	986 (82%)

Carbohydrate and Fat

The amount of protein catabolized each day having been estimated, the basal non-protein gaseous exchange could be calculated. From the volumes of gases involved in this non-protein metabolism, the amounts of carbohydrate and fat burned in the basal state were calculated. An additional daily allowance of fat was made to provide for the suprabasal requirements of physical activity, and the total amounts of body carbohydrate and fat burnt each way were estimated. Average

figures for each subject during the progress of starvation are given in Table III.

The estimated consumption of carbohydrate varied considerably among the different subjects, and cannot be regarded as being accurate, for reasons given under "Methods". However, in general the combustion of carbohydrate decreased rapidly during the first few days. The progressive cumulative losses are shown in relation to the loss of weight and loss of other fuel substances in Figures V, VI and VII. By the end of the period of starvation, it was estimated that Subject A had lost 673 grammes of carbohydrate in 18 days, Subject B 495 grammes in 28 days and Subject C 1050 grammes in 34 days (Table IV). Overall, the carbohydrate loss accounted for 3·5% to 11·0% of the total loss of weight and for 6·0% to 12·6% of the loss of weight excluding water, and provided 3·0% to 6·4% of the caloric needs.

The estimated weight of fat burnt each day was persistently high throughout starvation, apparently varying reciprocally with the caloric contributions made by protein and carbohydrate, and then declining gradually in parallel with the declining metabolic rate in prolonged starvation (Table III). The average daily losses during successive weeks were 219, 223, 214 and 203 grammes. The progressive cumulative losses are shown in Figures V, VI and VII and amounted, finally, to 4·1 kg. in 18 days in Subject A, 6·5 kg. in 28 days in Subject B, and 6·4 kg. in 34 days in Subject C (Table IV). Overall, loss of fat accounted for 44% to 68% of the total loss of weight and for 75% to 80% of the loss of weight other than water, and provided 87% to 90% of the caloric needs.

Basal Metabolic Rate

The basal metabolic rate during the first few days of starvation was not abnormal by usual standards. The average figures for subjects A, B and C were 90·6, 86·4 and 83·2 Calories per hour respectively, which are 111%, 103% and 107% of the values expected from the Harris-Benedict scales. The corresponding figures for the last few days of starvation were 82·1, 82·7 and 61·8 Calories per hour. The decrease in metabolic rate, as with the decreasing oxygen consumption, was proportionately greater than the changes in body weight and surface area.

Water

Loss of water from the body must account for the difference between the total loss of body weight and the sum of the losses of protein, carbohydrate and fat (the losses of calcium and other inorganic substances being assumed to be negligible). Estimations made in this way of the losses of water sustained by our subjects at different stages of starvation are included in Table III. There was a heavy loss of water in the first week. Subsequently smaller amounts were lost or water was actually retained. The progressive cumulative losses are illustrated in Figures V, VI and VII. The point of greatest loss was reached by Subject A on the ninth day, with an accumulated loss of about 4·4 litres, by Subject B on the thirteenth day with 6·2 litres, and by Subject C on the seventh day with 2·5 litres. At the conclusion of starvation the losses amounted to 3837, 5950 and 1159 ml. respectively (Table IV).

The net loss of water represented the difference between gains and losses of water. The amount of water gained each day from combustion of protein, carbohydrate and fat varied with the amounts of these substances catabolized, but averaged 236 to 287 ml. The total amounts of metabolic water produced in the three subjects are given in Table VI. The evaporative loss of water varied considerably. The average daily losses for the three subjects ranged from 720 to 1134 ml., which was the equivalent of 350 to 500 ml. per square metre of surface area. Evaporative losses were not consistently related to the metabolic rate or surface area. The total amounts of water evaporated are given in Table VI. Other gains (by ingestion and injection) and losses (in urine, fæces and blood) of water are more directly measurable. The

TABLE VI

Gains and Losses of Water (Grammes)

Subject	Duration (Days)	Gains			Losses			Net Loss
		Oral	Metabolic	Total	Urine, Fæces and Blood	Evaporative	Total	
A	18	16,200	5167	21,367	9480	15,625	25,105	3738
B	28	45,362	7580	52,942	27,300	31,743	59,043	6101
C	34	50,626	8021	58,647	35,442	24,490	59,932	1285

total amounts involved in these experiments are shown in Table VI, together with the differences between all gains and losses. Thus, the estimated net losses of water from the bodies of Subjects A, B and C were 3738, 6101 and 1285 ml. respectively. These estimates, based on measurements and calculations for the various contributing items in the water balance, differ by only 99, 151 and 126 ml. respectively

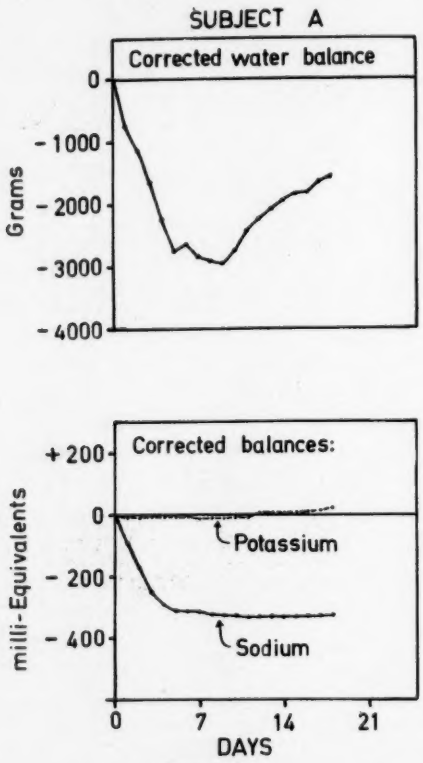

FIGURE VIII

The cumulative " corrected " water and electrolyte balances in Subject A, allowances having been made for the loss of cells

from those derived earlier from the measurements of weight loss (Table IV). The similarity of results increases the confidence which can be placed in the technical procedures involved in this study.

Further confirmation of the validity of the techniques employed comes from the results of measuring total body water in Subject C. The antipyrine spaces measured at the beginning of starvation and then on days 16 and 38 of the experiment were 35·3, 34·4 and 33·0 litres respectively. This indicates a loss of 0·9 and, finally, 2·3 litres. The estimated losses up to these times, based on the assessment of all gains and losses of water, were 1·46 and 2·50 litres.

The results so far mentioned relate to the total loss of water—that is, changes in the body content of water—and there can be little doubt

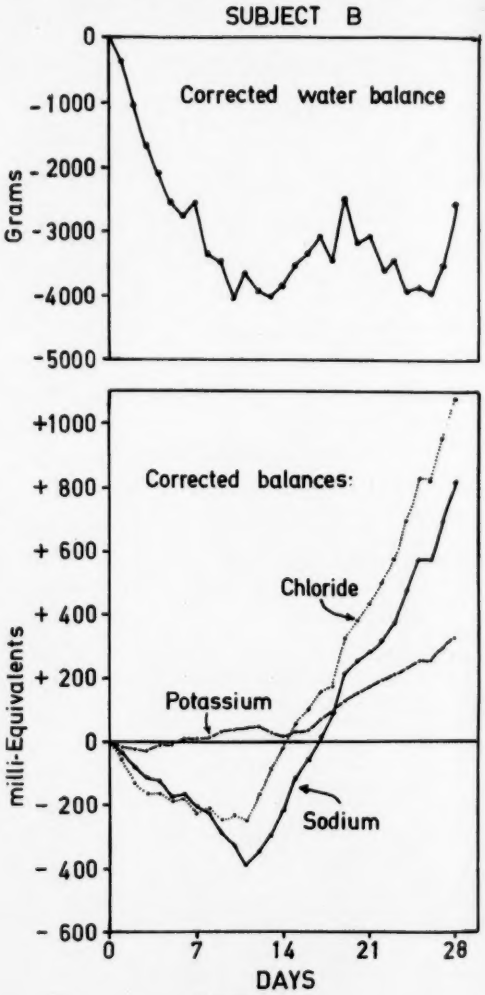

FIGURE IX

The cumulative corrected water and electrolyte balances in Subject B

about their general validity. A much more controversial topic is the location of the changes in body water in terms of the fluid compartments of the body. In the absence of actual measurements of these spaces definite conclusions cannot be reached, but inferences can be drawn from

some of our observations and from other published work, as will be discussed later. However, it is of value to assume that cells collapse and discharge their contained water and solutes in proportion to the amount of cellular protein catabolized, and to review the water balance with this concept in mind. The extracellular fluid (E.C.F.) would then gain water released from cells, in addition to the

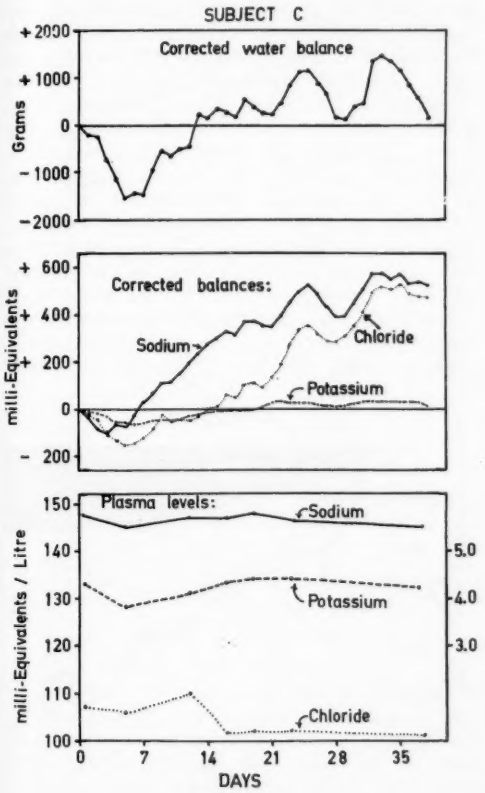

FIGURE X

The cumulative corrected water and electrolyte balances in Subject C

water gained from other sources already considered, and it would continue to lose water in the various ways listed previously. Any excess or deficiency in the volume of water required for maintaining a normal E.C.F. volume, and normal hydration of the remaining cell mass would presumably be shared, for osmotic reasons, by all compartments. We refer to the net result as the " corrected water balance ". Assessing the progressive changes in this way gave the " corrected water balance " illustrated in Figures VIII, IX and X for each of the three subjects. The maximum changes from the desirable volume of water present at the beginning of starvation were −3000 grammes in Subject A, −4000 grammes in Subject B and −1500 to +1400 grammes in Subject C. The changes estimated to have occurred by the end of starvation were −1626, −2633 and +1319 grammes respectively, as is shown in Table VII.

TABLE VII

The Corrected Water Balance (in Grammes)

Subject	Total Loss of Water	Water Released from Cells	Deviation from Desirable Body Water
A	3738	2112	−1626
B	6101	3468	−2633
C	1285	2604	+1319

This table also shows the magnitude of the volumes of water presumed to have been released from cells. This conception of water balance is further illustrated in Figures XI, XII and XIII, in which are shown the cumulative losses of cells (protein plus intracellular water), carbohydrate and fat, and

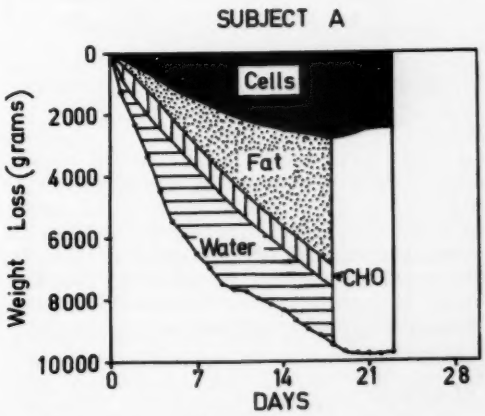

FIGURE XI

The progressive loss of " cells ", fat, carbohydrate and water comprising the weight loss in Subject A

variations in the corrected water balance in relation to the progressive loss of weight by the three subjects.

These calculations of corrected water balance assume that the subjects were in normal water balance at the beginning of starvation. The pre-starvation weight of Subject A had been steady for some days before the experiment,

so this is a reasonable assumption in her case, and the calculated negative balance is probably a reliable indication of a true departure from her normal state. However, Subject B put on 1·5 kg. in weight the day before starving commenced, so her reference line may have truly been at −1·5 kg. on Figure IX and her final calculated deficit would then have been −1133 grammes. In Subject C the body weight fell by 0·8 kg. immediately before the commencement of starvation, so that it is possible

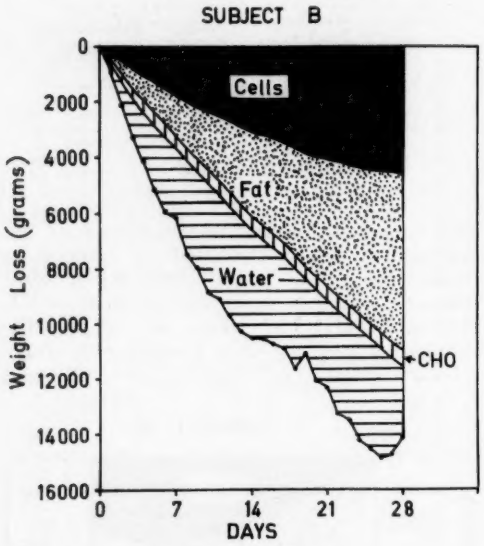

FIGURE XII
Cellular and other losses in Subject B

that she was already in negative balance on zero day. In that case, the reference line for water balance (Figure X) should be placed at +0·8 kg., giving a final calculated departure from the desirable normal volume of +519 grammes.

Electrolytes

Measurements were made of sodium and potassium in all three subjects and of chloride in Subjects B and C. Subject A received no electrolytes, while Subjects B and C were given accurately measured amounts of sodium, potassium and chloride (Approximately 140, 40 and 180 mEq respectively each day) either as tomato juice or as an aqueous solution. Very small amounts of calcium and magnesium were present in the tomato juice.

Minimal changes occurred in the serum levels, as is shown in Figures VIII, IX and X.

In calculating the electrolyte balances, we have again assumed that cells discharge their water and solutes in proportion to the amount of protein catabolized. The calculated balances therefore have as a normal base line a fixed extracellular load plus an intracellular load which is proportionate to the cell mass of the moment. Sodium and chloride balances, which take into account losses from the skin and the small intracellular amounts gained from cells as a result of protein catabolism, initially ran roughly parallel to the corrected water balance in Subjects B and C (Figures IX and X), but later became disproportionately positive, especially in Subject B after she changed from tomato juice to the aqueous solution of electrolytes. The apparent accumulation of sodium, potassium and chloride in this subject was progressive, and so enormous that suspicion naturally arose as to whether there were any analytical or other technical faults and whether she was discarding any of the solution. With careful checking, no sources of error were detected, and it is assumed that the electrolytes were being stored in some inaccessible tissue, perhaps bone. Subject C showed a similar

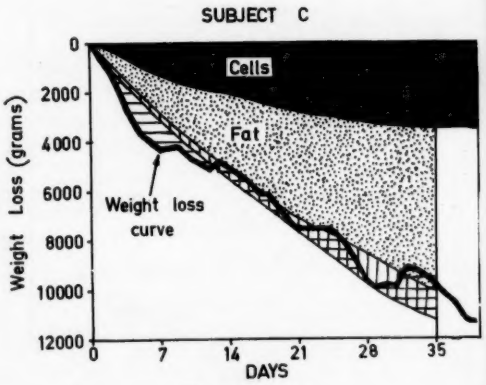

FIGURE XIII
Cellular and other losses in Subject C

positive storage, though of lesser degree. In Subject A, who lost electrolytes and received none, the negative water balance returned towards normal after 10 days, and yet the serum levels did not fall. It is possible that sodium and other electrolytes were released from bone in this case, as has been suggested elsewhere (Bergstrom and Wallace, 1954; Nichols and Nichols, 1956). This subject excreted large amounts of sodium for the first three days of starvation, and only small amounts thereafter—0·8 to 2 mEq per day (Figure IX).

There was excessive retention of potassium in Subject B, but in the other two subjects the corrected potassium balance was remarkably normal (Figures VIII and X). This was so only when account was taken of the potassium assumed to be released from cells in proportion to the catabolism of protein and extrusion of intracellular fluid. Figure XIV shows the marked difference in the balances for Subject C depending on whether or not cellular potassium is included in the calculations.

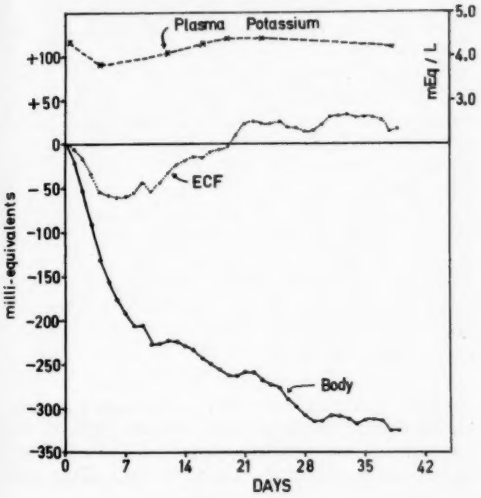

FIGURE XIV

The calculated cumulative potassium balances for the body as a whole and for the extracellular fluid in Subject C

DISCUSSION

Some of the general observations arising out of this study are of considerable interest, not only because of their physiological implications, but also because of their relevance to what patients not infrequently experience in a variety of clinical situations, particularly during treatment for obesity. The absence of hunger was a surprising finding, especially to the subjects themselves; but the same observation has been made by others who have used complete fasting or diets containing only 400 Calories in the treatment of obesity (Strong *et alii*, 1958; Bloom, 1959). Partial starvation, in which the caloric deficit is slight or moderate, is well known to give rise to prominent sensations of hunger and to cause thoughts to be concentrated on food. On this type of regime, which is the common one for treating the obese, patients are often sorely tempted by food and readily fall from grace. Only when the caloric deficit is very great and there is little or no food eaten does the sensation of hunger disappear. Our subjects were not at all tempted by food, and unconcernedly helped to serve other patients in the ward. This is a very chastening experience for an obese subject, and facilitates the acceptance of the subsequent low-calorie diet (500 Calories) and of the principles which underlie weight reduction. Moreover, it is important to realize that complete starvation, drastic though it sounds, did not induce any untoward symptoms beyond halitosis and sensitivity to cold, and did not incapacitate the subject.

Physically, starvation induced shrinkage of the body with rapid loss of weight, especially in the first week; but, again, no evidence of physiological distress was found in these studies. There was a loss of flesh and, according to our view of water balance, an excessive loss of water; but this caused no discernible discomfort or disability, and the composition of the body fluids remained in their normal limits. In general, then, homœostatis was preserved in spite of starvation, except for the loss of flesh, and it is important to know the nature of this loss more precisely.

Observations made in this study allowed of the weight loss being analysed in terms of its component elements, but this can be done in two ways. First, the weight loss can be regarded as being made up of the losses of protein, carbohydrate, fat and water, as illustrated in Figures V, VI and VII. There can be little criticism of this view. Secondly, the loss of weight can be regarded as being compounded of the losses of " cells ", carbohydrate, fat and water, as shown in Figures XI, XII and XIII. The second view assumes that when cellular protein is destroyed, its associated water is released. We favour this second view for reasons which will be stated later.

Excessive loss of water (over and above the loss of intracellular water associated with protein loss) was a feature of the first few days of starvation and accounted for up to 50% of the early loss of weight. The loss was not progressive, and at least in one subject it was subsequently restored even while starvation continued. After two or three weeks of starvation, this loss of water accounted, on the average, for about 24% of the weight lost. Carbohydrate contributed little to weight loss. Our observations have confirmed those of others (Benedict, 1907; Richardson, 1929), in showing that body carbohydrate is rapidly depleted in the first few days. It is believed that an average adult body contains about 400 grammes of carbo-

hydrate (Moore, 1959), but even after prolonged starvation carbohydrate is still to be found, perhaps derived from protein and fat (Lusk, 1917). The amounts of carbohydrate estimated to have been burnt by our subjects ranged from 495 to 1050 grammes, but the methods available do not allow a precise distinction to be drawn between carbohydrate and fat.

Protein-containing cells, involved in protein catabolism, provided a major contribution to the loss of weight in the early period of starvation, especially when few or no calories were available from carbohydrate to act as "protein-sparers". The loss of cells, derived largely from muscle, but also from liver, heart, adrenals, gonads and other tissues (Keys *et alii*, 1950), is heavy in the first few days. Thereafter it diminishes. By the end of starvation cellular losses had accounted for 30% to 40% of the total amount of weight loss by our subjects, and amounted to 2·8 to 4·6 kg. of "muscle". In contrast to the enormity of this loss of bulk, the cellular contribution to energy requirements was less than 7% of the total caloric turnover during the experimental periods. Three-quarters of the cellular loss was, of course, intracellular water. One of the major problems in starvation, whatever its context, is protein, or nitrogen, metabolism, and this is discussed in more detail later. Norethandrolone was effective as an anabolic or anti-catabolic agent in these subjects, reducing the protein breakdown and the liberation of cellular potassium.

Ultimately, the major contribution to weight loss comes from fat, and fat is the major contributor of calories throughout starvation. Loss of fat accounted for 44% to 68% of the total loss of weight in our subjects and for about 90% of the total caloric usage.

Water Balance

There is no doubt that water is lost from the body during starvation; but whether or not this should be regarded as normal and desirable, or abnormal and excessive, depends on the true nature of the "obesity tissue" which is obligatorily shed (to be discussed later) and on one's conception of normal water balance. We believe that body water should be lost to an extent which is dependent on the loss of cellular protein, but that the extracellular fluid volume should normally remain constant. We have used the term "corrected water balance" when interpreting our observations in this way. The maintenance of water balance, interpreted literally, would mean that gains and losses of water were equal, and that the total volume of water in the body remained constant. From this point of view, our subjects rapidly went into negative water balance in starvation, even to the extent of being "underhydrated" by six litres. However, a normal water balance as judged biologically might be quite different and would mean a normal or desirable amount and distribution of water in the body relative to the solid tissues.

The total amount of water in the body is closely related to the mass of lean body tissue, so that if lean tissue is lost, a decrease in the total body water may be expected. This is what occurs, and is well illustrated by our observations and generally accepted. What is more controversial is the source of the lost fluid; but the consensus of published work would suggest that it is the intracellular fluid which shrinks, while the extracellular fluid remains constant. Moore *et alii* (1956) measured the thiocyanate space in 10 starved people and found it to be 101% of what would be expected in their normal healthy state. The data of Beattie *et alii* (1948) showed the thiocyanate space in starved persons to be slightly larger than the expected figure for their height and age; but they were studying famine œdema, and some of their subjects were frankly œdematous. Sunderman (1947) found a thiocyanate space of 14·7 kg. in a man who had fasted for 45 days and lost about 30% of his pre-starvation weight. After he had been re-fed for 43 days, it was 14·6 kg. Keys and his colleagues (1950) measured the thiocyanate space during semi-starvation in their Minnesota experiment, but gave the results as percentages of body weight and did not give the actual values for either volumes or body weights. Thus, they state that the E.C.F. volume increased from 23·5% to 34% after the loss of 25% of the initial body weight. For a man whose original weight was 70 kg., this would indicate an increase in E.C.F. volume from 16·4 to 17·8 litres during the loss of 17 kg. of body weight. After rehabilitation for several months, the thiocyanate space was found to be virtually identical with the pre-starvation value. In a later article (Keys *et alii*, 1955), reference is made to the relative constancy of the extracellular space during the Minnesota experiment. Measurements of the intravascular component of the E.C.F. during undernutrition also show no evidence of a significant change (Beattie *et alii*, 1948; Sunderman, 1947; Keys *et alii*, 1950; Walters *et alii*, 1947; Perera, 1946; Henschel *et alii*, 1947; Mollison, 1946).

The evidence is in favour of a constant volume of E.C.F. in spite of variations in the fleshy bulk of the body. This supports the contention

of Fourman and McConkey (1958) that the loss of weight which occurs in starvation is associated with collapse rather than shrinkage or reduction in numbers of cells. Consequently, the total surface area of cells remains virtually unchanged, as does the film of fluid which provides the major portion of the E.C.F. Since the total body water decreases during starvation, but the E.C.F. volume remains constant, the loss of water must be from the intracellular compartment.

Histological studies show that cells shrink during starvation, but that their numbers do not decrease unless starvation is severe and prolonged (Keys *et alii*, 1950). Fat, protein and glycogen are lost. Analyses of fatty tissue show the presence of water (5% to 50%), but this includes the extracellular water present in the tissue and the intracellular fluid which is associated with protein in the nucleus and membrane of the fat-containing cells (Moore, 1959). It is generally believed that neutral fat is stored in an anhydrous state, and that its discharge does not involve the release of any water (Moore, 1959). There are claims that glycogen is associated with three times its weight of water, and that the water is released when glycogen is burnt (Newburgh *et alii*, 1929–1930).

However, Investigation of this point (Bridge and Bridges, 1932) has shown that the evidence is far from conclusive, and it seems best to ignore this possible cause of liberation of cellular water in starvation, especially as the glycogen stores become exhausted within a few days. Protein breakdown, on the other hand, would seem to be extremely likely to result in the discharge of cellular water. The observed shrinkage of proteinaceous cells during starvation would suggest it, and the hygroscopic nature of protein makes it likely. Newburgh *et alii* (1929–1930) accepted it and included it in their extensive investigations of water metabolism, and so have numerous workers up to the present time (Moore, 1959; Gamble, 1951). A generally accepted relationship is 3 grammes of water to 1 gramme of protein. Peters and Lavietes (1933) critically examined the available evidence on this and related aspects of water metabolism, and came to the conclusion that there was little support for any definite relationship between protein and water. They were critical particularly of any idea that water was "bound" to protein, but conceded the possibility of intracellular water being restrained by protein by some physiological force, and yet sharing in the fluctuations which occur in body water as a whole.

Support for the "cell release" concept can, we believe, be marshalled from the results of the present investigation, as well as from other studies in starvation. The decrease in body water experienced by our subjects was large, up to 6·2 litres (perhaps 18% of the original total body water), and yet there were no symptoms or signs of distress. Lack of thirst and the maintenance of normal values for hæmatocrit and serum electrolytes suggest that neither the cells nor the extracellular compartment were underhydrated to any extent. The situation appears more reasonable if we imagine that a portion of the intracellular contents—protein, water and electrolytes—was amputated and discarded, and that this accounts for some of the observed losses. When allowance has been made for cell water lost in this way (2·2, 2·5 and 3·3 kg.), the deviations from normal of the remaining water content (corrected water balances of −1·6, −2·6 and +1·3 kg.) are more acceptable, especially if a further adjustment is made for possible imbalances existing at the beginning of starvation (giving corrected water balances of −1·6, −1·1 and +0·5 kg.). The curve of the water losses, being steepest early in starvation when protein breakdown is greatest, would be in accord with progressive amputation of cells. Finally, the potassium balances make better sense when it is assumed that the amputation of cells involves electrolytes as well as water and protein.

Similar conclusions may be drawn from the observations made by Passmore *et alii* (1958) over a period of six weeks of semi-starvation in seven obese subjects (Table VIII). Their subjects lost water to the extent of 1·3 to 3·7 litres. However, if the results are recalculated and an allowance is made for the cell losses, then the corrected water balances range from −1·8 to +1·4 litres and average −100 ml. per person. As the subjects were in apparently good health after a long period of observation, one would expect them to be in normal—that is, desirable—water balance. The result would agree with the hypothesis that the desirable water content during undernutrition is made up of a normal extracellular volume plus a reduced intracellular volume, and that the reduction is proportional to the protein loss, as though an entire portion of cellular material was amputated.

All things considered, it would seem to be an advantage to consider the "desirable water balance" in the manner described; but confirmation of its validity must await the results of further work in which water-compartments are to be measured. Superimposed on these

TABLE VIII

Average Daily Losses in Partial and Complete Starvation[1]

Series	A. Calories	B. Fat (Grammes)	C. Carbo-hydrate (Grammes)	D. Protein (Grammes)	E. Total Water (Grammes)	F. Cells (Grammes)	G. Excess Water (Grammes)
I. Passmore *et alii* (1958); 7 subjects, partial starvation:							
(i) Total period (42–45 days) ..	2700	282	—	19	61	78	2
(ii) First 2 weeks	2900	298	—	34	178	137	74
II. Present study; 3 subjects, more drastic starvation:							
(i) Total period (18–34 days) ..	2200	213	28	34	137	136	35
(ii) First 2 weeks	2400	221	30	46	274	182	138

[1] The figures in columns F and G are derived from those in D and E by allowing for the water associated with protein in cells.

changes in water content, which are an integral part of starvation, there will, of course, be fluctuations due to osmotic, acid-base and other factors such as are commonly observed even under ordinary conditions (Robinson, 1960). Another possible source of confusion is the water contained in the intestinal tract. This is included in the total body water as measured by the usual dilution techniques; but it should really be regarded as a concealed "external" reservoir of water, which may presumably be drawn upon by the body proper.

These considerations are of more than academic interest, particularly in the anuric patient, whose treatment is aimed at preserving a desirable water balance. Any deviation from the desirable balance may be regarded as being equal to the difference between gains and losses, where the gains include ingested water, metabolic water and water released from cells, while the losses include the water of urine, fæces, evaporation and blood which is lost.

"*Obesity Tissue*"

Substances which comprise the excess bulk carried by obese subjects and shed by them when they reduce weight can be regarded as "obesity tissue". What is the nature of obesity tissue? Obviously fat is a major component, carried intracellularly in adipose tissue; but it is conceivable that protein and water may accompany it as cellular structures and as free or bound fluid. Losses and gains of fat and protein are relatively easily assessed; but it is difficult to estimate the amount of water truly associated with obesity tissue, because of the considerable fluctuations in hydration of the body which occur even under ordinary circumstances.

Keys *et alii* (1955) reported that the gain in weight produced by over-feeding was made up of 62% fat, 0% to 1% glycogen, 24% cellular tissue (protein and intracellular fluid) and 14% extracellular fluid, with a calorific value of 6180 Calories per kilogram. Brozek *et alii* (1957) found that the composition of the weight loss with under-feeding varied with the stage of undernutrition, and also with the caloric intake; thus the loss varied from 25% fat, 5% protein and 70% water and 3000 Calories per kilogram in the first few days to 85% fat, 15% protein and 0% water and 8700 Calories per kilogram after 22 days. Passmore *et alii* (1958) analysed the composition of the obesity tissue lost by seven patients consuming diets containing about 400 Calories per day over periods of 40 to 45 days. Their general conclusion was that obesity tissue varied in composition in different circumstances, but in their study it comprised 73% to 83% fat, 4% to 7% protein and 10% to 23% water. In these terms, our own results for three subjects starved for periods of 18 to 34 days are 50% to 79% fat and carbohydrate, 8% to 9% protein and 12% to 42% water. It is valuable to compare in greater detail our results with those of Passmore *et alii* over the initial periods of observation as well as over the entire periods. This we have done in Tables VIII and IX. Our results pertain to complete or almost complete starvation, whereas the others relate to partial starvation over longer periods. We have recalculated the data of Passmore *et alii* in terms of protein-containing cells and deviations in the desirable water balance according to the methods used in the present study. Considerable variation exists among different subjects, but only the average figures are given in the tables.

Passmore's subjects were encouraged to be active and had a daily energy expenditure of 500 Calories more than our subjects. Obvious generalizations from Table VIII are that protein breakdown was greater in the first fortnight of starvation than later, and that it was greater in completely starved subjects than in those

TABLE IX

Percentage Composition and Calorific Value of "Obese Tissue" Lost in Starvation

Series	Total Loss of Weight				Loss of "Flesh"		
	Fat and Carbohydrate	Cells	Water	Calories per Kilogram	Fat and Carbohydrate	Cells	Calories per Kilogram
I. Passmore *et alii* (1958):							
(i) Total period (42–45 days) ..	78%	21%	1%	7470	78%	22%	7480
(ii) First 2 weeks	58%	27%	15%	5670	68%	32%	7550
II. Present study:							
(i) Total period (18–34 days) ..	59%	33%	8%	5820	64%	36%	6320
(ii) First 2 weeks	44%	32%	24%	4420	58%	42%	5760

who received 400 Calories daily. It would appear from the figures for the first two weeks that the feeding of 400 Calories caused protein-sparing to the extent of 25%. The average amount of water lost each day was greater early in starvation than later, and it was greater in those who starved completely. These differences were even more pronounced for the corrected water balance—that is, the remaining water loss after allowances had been made for the water released from cells as a result of protein breakdown. There was no clear relationship between the excess water loss and the amounts of fat, carbohydrate and protein catabolized such as might suggest revising the protein-water relationship (1 : 3) used here, or that preformed water was released by the destruction of carbohydrate and fat (Newburgh *et alii*, 1929–1930). It would be impossible to be certain on this point. The excessive water loss in complete starvation could have been due to emptying of gut-water, or to an obligatory loss associated with the excretion of ketones.

That the composition of obesity tissue varies in different circumstances, as was remarked by Passmore *et alii*, is well exemplified by the foregoing discussion, which is further illustrated in Table IX. The calorific value of the tissue is considerably influenced by the water component and by the levels of energy expenditure and protein destruction; it is most satisfactorily related to "flesh"—that is, fat, carbohydrate and cellular tissue—exclusive of any additional fluid participation. In this regard, it is noteworthy that our recalculation of the data of Passmore *et alii* shows a negligible change (1% of the total loss of weight) in the corrected water balance at the end of their 42 to 45 days of observation; that is, their subjects were in correct water balance. This suggests that obesity tissue need not include water, other than the water included in protein-containing cells which are lost. As for the protein content of obesity tissue, this will depend on any changes which occur in the size of the labile pool of protein when weight is lost, on compensatory adjustments in the muscle mass which might have hypertrophied previously to cope with the excess body weight, as well as on any cellular material which is an essential part of obesity tissue. However, it is conceivable that nitrogen balance may be preserved by a properly constituted diet, even though deficient in calories, in which case the obesity tissue being lost would consist of nothing but fat.

Nitrogen Metabolism

Our observations regarding the nitrogen loss in complete starvation are in accord with those made by other workers (Benedict, 1907, 1915). For the first day or two nitrogen loss may be depressed, but it then rises rapidly and may exceed the pre-starvation rate. Thereafter, it progressively falls to reach a floor-level which may be as low as 2 to 5 grammes of nitrogen per day. The rate of fall is greatest in the first week. The magnitude of the loss is greater in those who have previously consumed a diet rich in protein, and it is greater in lean persons than in the obese (Munro, 1951). It has been suggested (Benedict, 1915) that the initial fall in nitrogen loss is due to the protective, or protein-sparing, effect of the glycogen stores, which become depleted in a day or two. The subsequent slower diminution in nitrogen loss is attributed to depletion of the "labile body protein" (Whipple, 1956); but the size and location of this hypothetical pool is unknown, and "lability" may mean that some tissues are relatively unstable and readily catabolized rather than indicating the presence of a dispensable store of protein.

The consumption of food is obviously an important factor in sparing tissue protein and minimizing nitrogen imbalance. It is known (Lusk, 1917) that nitrogen balance can be maintained in dogs by feeding protein alone, providing the ingested protein supplies at least

50% of the total caloric requirements. The quantities of protein involved are large, and probably exceed the human masticatory ability. The addition of fat and carbohydrate to the diet reduces the amount of protein required for nitrogen balance. This is not attributed solely to the provision of non-protein calories, as carbohydrate is much more effective than fat. Protein-sparing is roughly proportional to the amount of carbohydrate supplied up to about 100 grammes (400 Calories), but above this there is little further gain and no marked distinction between carbohydrate and fat (Zeller, 1914; Munro, 1951). Carbohydrate feeding causes a lowering of the level of amino-acids in the blood, probably as a result of enhanced protein synthesis, but also, perhaps, because of decreased protein catabolism. The body has a constant demand for glucose, which, if not available from stores or ingestion, would conceivably have to be derived from protein, thereby causing loss of nitrogen. The brain, for example, metabolizes glucose exclusively to the extent of about 100 grammes daily (Lassen, 1959). In complete starvation, it would seem to be impossible to maintain nitrogen balance even for short periods.

Given some caloric intake, then, nitrogen balance can be maintained over a wide range of protein intake (Chittenden, 1904). The lower limit is of considerable interest, but is ill-defined. Experiments have been described in which nitrogen balance occurred with an intake of 4 to 8 grammes of nitrogen per day (Chittenden, 1904; Siven, 1900). At these low levels the quality of the protein becomes increasingly significant, and minimal nitrogen intake should be assessed in relation to the amino-acids to which it belongs. Thus Rose (1949) has shown that a minimum of 0·7 gramme of nitrogen in the form of essential amino-acids is required for the maintenance of balance when the total nitrogen intake is 10 grammes per day, the excess being composed of glycine and urea from which the non-essential amino acids can be synthesized. Rose and Wiscon (1955) subsequently preserved nitrogen balance in two men with an intake of only 3·5 grammes of nitrogen per day derived from effective essential amino acids (1·42 grammes nitrogen), ineffective essential amino acids (0·52 gramme N_2), glycine (1·21 gramme N_2) and nitrogen of undetermined composition (0·35 gramme). It seems probable that the minimum intake could be even lower, 2·28 to 2·55 grammes, if its component amino acids are judiciously selected.

In our starved subjects, nitrogen catabolism was finally reduced to 2 to 4 grammes per day. A further reduction occurred in one subject when she was given 500 Calories of carbohydrate daily, which was probably sufficient to stop the production of carbohydrate from protein. Giving protein to two of our subjects caused an immediate change to a positive nitrogen balance, which then became progressively less positive and then negative again in one of them. This suggests that, in spite of a markedly negative caloric balance, protein could be stored or synthesized to some extent, which was perhaps dependent on the supply of essential amino acids.

Quite apart from the contraction of labile stores and the sparing effect of other foodstuffs, hormones may play a part in determining the pattern of nitrogen loss in starvation. Cortisone is known to increase nitrogen loss, probably as a result of increased protein catabolism; but the urinary excretion of steroids is not increased in starvation (Sunderman, 1947; Bloom, 1959). Male sex hormones exert a powerful, though often temporary, anabolic effect on protein metabolism (Geiger, 1960), but there is no certainty that the endogenous hormone plays an influential part. The production of androgens is decreased during starvation, and returns rapidly to normal after resumption of a normal diet (Sunderman, 1947; Keys *et alii*, 1950), and there is a positive correlation between the level of protein intake and the urinary excretion of androgens, at least in Nigerians (Edozien, 1960). The effectiveness of these hormones in decreasing nitrogen loss, even in starvation, suggests that anabolism is encouraged, or that by some interrelated means catabolism is suppressed. Norethandrolone was effective in our subjects at both high and low levels of nitrogen loss, early and late in starvation this is contrary to the claim that it exerts its effect only when the nitrogen turnover is heavy (Stokes *et alii*, 1959).

The basic nitrogen catabolism may represent obligatory "wear and tear". Under these conditions, the nitrogen losses are found in urea ammonia, uric acid and creatinine. Reduction is evident mainly in urea. Uric acid excretion fluctuates under varying metabolic conditions and is not clearly predictable. Ammonia varies in relation to acid-base requirements. Creatinine, on the other hand, is excreted at a relatively constant rate, and warrants further consideration for the part it may play in determining the minimum rate of nitrogen loss.

Creatinine and Creatine Excretion

It has been shown (Bloch *et alii*, 1941; Sandberg *et alii*, 1953) that creatinine is formed from creatine by a simple chemical process

that does not involve enzymic action or energy, and that the rate of conversion *in vivo* is similar to that which occurs *in vitro* in an aqueous solution resembling the normal body fluids. Creatinine excretion, therefore, should depend solely on the amount of creatine in the body, provided that renal function is normal and that no creatine or creatinine is being ingested. Almost all the creatine is to be found in muscle. During starvation, creatinine excretion gradually decreases. This is not due to impaired renal excretion, as the creatinine clearance remains normal, and it is reasonable to attribute it to a decreased body content of creatine.

There is no doubt that muscle mass, and presumably body creatine, decrease during starvation; but there is no way of accurately determining the loss of muscle in the intact person or, indeed, even in the dissected animal, because of the difficulty of quantitatively measuring both skeletal and plain muscle. However, if it is assumed that all the nitrogenous losses are derived from muscle, then an estimate of the amount of muscle lost can be made, and a comparison with the amount of creatinine excreted will show any disproportion suggestive of creatine depletion of muscle. Normally each gramme of non-collagenous nitrogen in muscle is associated with 0·138 gramme of creatine (Baldwin *et alii*, 1952), and it is the non-collagenous nitrogen which is depleted in starvation (Hagan and Scow, 1957). Creatine is hydrolysed at a steady rate of about 2% per day (Sandberg *et alii*, 1953; Hoberman *et alii*, 1948; Bloch *et alii*, 1941), and there is no reason to believe that this may alter during starvation.

Subject C lost 140 grammes of nitrogen which, had it all been derived from muscle, would have caused the total body creatine content to decrease by 19·3 grammes, leaving the remaining muscle with a normal creatine concentration. This loss from the creatine pool should have caused a decrease in the daily creatinine excretion of 380 mg. The actual measured decrease was only 200 mg. per day. Thus, the decrease in creatinine excretion was less than expected, implying that the creatine content of the remaining muscle was abnormally high (which is unlikely), or that something less than 100% of the total nitrogen loss came from muscle. If it is assumed that muscle content was normal, it can be calculated that muscle supplied 52% of the total nitrogen loss, which is higher than has been concluded from animal experiments (Keys *et alii*, 1950).

In Subject B, the observed decrease in daily creatinine excretion was 800 mg., whereas it would have been only 550 mg. had all the nitrogen loss been derived from muscle. This is evidence that the creatine content of the remaining muscle was subnormal, as a result of either decreased creatine synthesis or a storage defect in muscle. A similar conclusion was reached for Subject A, in whom the observed decrease in creatinine excretion, 340 mg., exceeded the hypothetical decrease, 280 mg. It is of interest that both these subjects received practically no calories, whereas Subject C was on a steady ration of 100 Calories in the form of carbohydrate. Benedict's (1915) subject Levanzin, who ingested nothing but distilled water for 31 days, lost 276 grammes of nitrogen, which, had it been derived entirely from muscle, would have meant a loss of 38 grammes of creatine and a decrease in the daily excretion of creatinine of 700 mg. The observed decrease was 700 mg. Since it is most unlikely that all the nitrogen lost came from muscle, the conclusion here also is that the remaining muscle tissue was somewhat depleted of creatine.

Whether there is any abnormality of production or storage of creatine or excessive leakage or breakdown is not clear. From the nature of the experiments, decreased production would seem likely. However, in the present study and in others dealing with starvation (Duncan, 1959), creatine itself appeared in the urine in increased amounts. This also occurs in muscular dystrophy, in which it has been shown that creatine production is normal or supernormal, but a muscle defect prevents storage (Benedict *et alii*, 1955). A similar defect may occur in starvation.

If the synthesis of creatine continues in starvation, then this can be achieved only if other tissue proteins are raided for the necessary amino acids. On the template theory of protein synthesis, protein is formed as an all-or-none affair, and incomplete proteins cannot exist and are burnt (Munro, 1951; Geiger, 1960). Thus, fragments remaining after creatine synthesis would be deaminated and excreted unless they combined to form simpler proteins. It is possible that some of the nitrogenous losses occurring at minimal levels of nitrogen metabolism are derived in this way.

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IDIOPATHIC HÆMOCHROMATOSIS—A FAMILY STUDY[1]

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SUMMARY

The plasma iron concentration and plasma total iron-binding capacity were determined and a series of liver function tests performed on the plasma from the immediate relatives of 23 patients with idiopathic hæmochromatosis. Abnormal iron transport values were found in 27% of the 70 relatives, but only two relatives gave abnormal results to the liver function tests. The results were considered to be compatible with a mode of inheritance of hæmochromatosis previously suggested by other authors—by a non-sex-linked dominant gene. It was suggested that relatives of patients who are found to have abnormally high plasma iron levels should be treated by venesection, whether or not they show other evidence of hæmochromatosis.

SHELDON (1934, 1935) was the first to suggest that idiopathic hæmochromatosis was an inherited inborn error of metabolism. In his review of the literature up to that time he found five proven instances of the fully-developed disease in more than one member of a family. In the next twenty years, reports of only seven familial cases were published (Finch and Finch, 1955). To these Finch and Finch added two more. However, since this review in 1955, at least 18 further instances of familial occurrence of hæmochromatosis have been described (Pirart and Catez, 1954; Kleckner *et alii*, 1955; Houston and Zilkha, 1955; Keppeler, 1956; Houston, 1957; Debré *et alii*, 1958; Pirart and Gatez, 1958; Cohen and Bothwell, 1958; Conte *et alii*, 1958; McAlpine, 1959; Bothwell *et alii*, 1959; Dillingham, 1960). In addition to the familial occurrence of hæmochromatosis, further evidence as to the inherited nature of the disease has been provided by estimations of the serum iron concentration of relatives of patients with the disease. Debré *et alii* (1952, 1958), Finch and Finch (1955), Pirart and Gatez (1958) and Bothwell *et alii* (1959) found that about 20% of immediate relatives had elevated serum iron values. On the basis of the familial incidence of the disease and the high proportion of relatives with abnormal serum iron levels, it has been proposed that hæmochromatosis is due to a dominant gene (Neel and Schull, 1954; Debré *et alii*, 1958; Bothwell *et alii*, 1959).

This paper describes the results obtained in a systematic study of the immediate relatives of 23 patients with hæmochromatosis. The plasma total iron-binding capacity was estimated and a series of liver function tests were performed, in addition to estimation of the plasma iron concentration. In hæmochromatosis the plasma iron-binding capacity is usually depressed (Laurell, 1952; Finch and Finch, 1955), and alterations in the results of liver function tests are commonly observed (Finch and Finch, 1955). It was hoped that these investigations would provide further evidence on the pattern of iron transport values in relatives of hæmochromatotic patients, and on whether alterations in liver function occurred in the relatives in the presence or absence of elevated plasma iron values.

MATERIALS AND METHODS

All the proven cases of idiopathic hæmochromatosis known to have been diagnosed in Perth in the last five years were studied. Diagnosis was based on the usual clinical and biochemical features, and was confirmed either by histological examination of the liver or by response to treatment by repeated venesections.

A family history was obtained from each patient and his siblings. Special note was taken of the occurrence of consanguinity of the patients' parents, the occurrence of other cases of hæmochromatosis or any of its symptoms and the age and cause of death among relatives of the patients. The patients and relatives were questioned directly as to any history of excessive consumption of alcohol.

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Biochemical investigations were carried out on 70 relatives of the patients (13 brothers, 16 sisters, 18 sons and 23 daughters). In every case the following estimations were made: plasma iron content and total iron-binding capacity (method of Morgan and Carter, 1960); plasma albumin content and plasma globulin content (Kingsley, 1942); plasma bilirubin content (Powell, 1944); plasma alkaline phosphatase content (King and Wootton, 1956); thymol turbidity and thymol flocculation (Maclagan, 1944) and zinc sulphate turbidity (Kunkel, 1947). Since there is a well-recognized diurnal variation in the plasma iron concentration with the highest values in the morning (Laurell, 1952), all blood specimens from patients, relatives and control subjects were obtained between 9 and 11 a.m. The only immediate relatives on whom the above-mentioned tests were not performed were those who refused to submit to venepuncture (five relatives), and those who lived outside of Western Australia or in distant areas of the State where suitable arrangements for collection of the blood samples could not be made (32 relatives).

Plasma iron and iron-binding capacity values were estimated for 35 healthy male and 35 healthy female subjects, chosen at random from hospital and unversity personnel, and aged 17 to 55 years. The "normal range" for plasma iron content, total iron-binding capacity and percentage saturation of the iron-binding capacity, were calculated from these results as the mean ± 2 standard deviations from the mean; values falling outside this range have been called "abnormal".

RESULTS

Hæmochromatosis Patients

The clinical features were similar to those found in most series of cases of hæmochromatosis (Table I). Thus there was a marked difference in sex incidence (21 males and two females), and the age of presentation was in all cases more than 40 years. Hepatomegaly and abnormal

TABLE I

Clinical Features and Evidence for the Diagnosis in 23 Cases of Idiopathic Hæmochromatosis

Case Number	Patient's Sex and Age (Years)	Clinical Features			Evidence of Diagnosis		
		Hepatomegaly	Skin Pigmentation	Diabetes Mellitus	Liver Biopsy	Autopsy	Response to Venesections
1	M.: 47	+	+	−	+		
2	M.: 48	+	+	+	+	+	+
3	M.: 48	+	+	−	+	+	+
4	M.: 52	+	+	−	+		+
5	M.: 58	+	+	+	+		+
6	M.: 54	+	+	+	+		+
7	M.: 52	+	+	+	+		
8	M.: 69	+	+	+		+	
9	M.: 62	+	+	+	+		
10	M.: 76	+	+	−		+	
11	M.: 62	+	+	+			+
12	M.: 69	+	+	+			+
13	M.: 56	+	+	+			+
14	M.: 49	+	+	+			+
15	M.: 45	+	+	+			+
16	M.: 54	+	+	+			+
17	F.: 64	+	+	+	+		+
18	M.: 65	+	+	+			+
19	M.: 57	+	−	−	+		
20	F.: 62	+	+	−		+	
21	M.: 71	−	+	−	+		+
22	M.: 64	+	+	−	+		+
23	M.: 48	+	+	−	+		+

skin pigmentation were found in almost all cases (22 of the 23), but diabetes mellitus occurred less commonly (14 of the 23 cases). The results of the plasma iron and total iron-binding capacity estimations were typical of hæmochromatosis, with elevation of the plasma iron values above the normal range in all but one and depression of the total iron-binding capacity in seven of the 18 patients on whom these tests were performed (Table II). The results of the liver function tests were somewhat unusual, however, because of the high incidence of abnormal results (17 of 19 patients on whom liver function tests were performed). Finch and Finch (1955) stated that abnormal results to liver function tests were found only in about 50% of patients with hæmochromatosis.

Family Histories

No instances of consanguinous marriage or family histories of hæmochromatosis were obtained. In two cases (8 and 21) abnormal skin pigmentation was found in a relative, and in three cases there was a family history of diabetes mellitus (8, 18, 21). Only six patients admitted to excessive consumption of alcohol.

Plasma Iron and Iron-Binding Capacity Values

The normal values for plasma iron, total iron-binding capacity and percentage saturation are shown in Table III. The results for the relatives of hæmochromatosis patients are presented in Table IV. Debré *et alii* (1958) found that the mean plasma iron concentration

TABLE II

Plasma Iron Concentration, Total Iron-Binding Capacity and Percentage Saturation of the Iron-Binding Capacity and Results of Liver Function Tests in 23 Cases of Idiopathic Hæmochromatosis

Case Number	Plasma Iron Concentration (µg. per 100 ml.)	Plasma Total Iron-Binding Capacity (µg. per 100 ml.)	Percentage Saturation of the Iron-Binding Capacity	Plasma Albumin Concentration (Grammes per 100 ml.)	Plasma Globulin Concentration (Grammes per 100 ml.)	Plasma Bilirubin Concentration (mg. per 100 ml.)	Plasma Alkaline Phosphatase Concentration (King-Armstrong Units per 100 ml.)	Thymol Turbidity (Units)	Thymol Flocculation (Units)	Zinc Sulphate Turbidity (Units)
1	205	205	100	1·9	4·9	3·0	7·7	5	++	15
2	285	285	100	3·3	4·9	0·6	7·3	3	0	3
3	—	—	—	3·5	5·6	0·4	13·1	7	+++	8
4	290	290	100	—	—	—	—	—	—	—
5	260	260	100	3·6	3·8	0·4	12·0	6	++	3
6	191	245	78	4·0	3·0	0·3	12·7	2	0	—
7	274	281	97	—	—	—	—	—	—	—
8	—	—	—	—	—	—	—	—	—	—
9	—	—	—	3·8	5·6	0·9	13·0	2	0	18
10	—	—	—	3·0	4·0	9·4	23·0	5	0	10
11	235	235	100	2·1	5·3	—	—	—	—	—
12	280	280	100	2·7	4·7	0·3	30·3	4	0	2
13	270	300	90	4·2	3·3	0·3	9·0	2	+	3
14	393	393	100	3·2	5·1	0·3	10·0	2	+	6
15	242	242	100	3·2	3·8	0·2	5·0	2	+++	5
16	239	264	91	3·5	4·0	0·2	12·9	1	0	1
17	263	330	80	4·0	4·0	0·4	10·3	3	++	2
18	—	—	—	—	—	—	—	—	—	—
19	195	182	107	2·6	3·9	0·4	5·0	0	0	—
20	174	174	100	2·9	4·3	0·9	9·0	0	0	—
21	242	254	95	3·7	4·5	0·2	8·5	1	0	—
22	226	250	90	2·9	4·0	1·2	5·2	0	—	—
23	368	370	99	4·2	4·5	1·1	6·4	0	—	—
Means ..	257·5	267·2	96·4	3·28	4·38	3·89	11·28	2·50	—	4·22

TABLE III

Plasma Iron Concentration, Total Iron-Binding Capacity and Percentage Saturation of the Iron-Binding Capacity for 35 Normal Male and 35 Normal Female Subjects

	Normal Males			Normal Females		
	Plasma Iron Concentration (µg. per 100 ml.)	Plasma Total Iron-Binding Capacity (µg. per 100 ml.)	Percentage Saturation of the Iron-Binding Capacity	Plasma Iron Concentration (µg. per 100 ml.)	Plasma Total Iron-Binding Capacity (µg. per 100 ml.)	Percentage Saturation of the Iron-Binding Capacity
Mean	127	334	38·1	114	329	34·7
Standard deviation	28·7	40·6	9·91	32·6	40·1	10·81
Normal range ..	70–185	253–415	18·8–58·5	58–179	249–409	13·2–56·4

for sons over the age of 15 years was much higher than it was for sons under the age of 15 years. For this reason the results for sons and daughters have in Table IV been subdivided into groups relating to ages less than or more than 15 years.

TABLE IV

Plasma Iron, Total Iron-Binding Capacity and Percentage Saturation of the Iron-Binding Capacity Values for the Relatives of Patients with Idiopathic Hæmochromatosis (Mean Values∓Standard Deviation of the Mean)

Group	Number of Subjects	Plasma Iron Concentration (µg. per 100 ml.)	Plasma Total Iron-Binding Capacity (µg. per 100 ml.)	Percentage Saturation of the Iron-Binding Capacity
Brothers	13	158 ∓65·82	324·2∓63·42	48·7∓25·83
Sisters ..	16	140·6∓40·50	306·0∓42·15	48·1∓19·52
Sons :				
Aged under 15 years	5	125 ∓41·60	363·8∓39·65	35·4∓15·01
Aged over 15 years	13	155·8∓65·71	314·0∓32·99	50·5∓25·77
Total	18	147·0∓69·9	328·0∓43·18	46·3∓23·90
Daughters :				
Aged under 15 years	5	112·7∓35·13	339·5∓55·55	34·2∓24·35
Aged over 15 years	18	110·6∓50·45	362·2∓67·97	32·7∓18·26
Total	23	110·8∓44·46	358·0∓66·05	33·9∓16·82

An abnormal increase in plasma iron concentration was found in 14 relatives of patients (20%). These relatives consisted of five brothers, four sisters, four sons and one daughter. No significant differences ($P>0·05$) were found between the means of any group of relatives and the means of the control subjects. This applied in the case of sons and daughters, whether the tests for significance of the differences were applied to the results of the whole groups or only to the results of the sons or daughters older than 15 years. The plasma total iron-binding capacity was abnormally low in the case of only one relative (a sister), and there were no significant differences between the mean results of the groups of relatives and the controls. The percentage saturation was increased above the normal range in the case of 18 relatives (five brothers, five sisters, seven sons and one daughter). This represents 26% of all the relatives studied. However, a statistically significant difference was found only between the means of results for sisters and for control females ($P<0·02$). A total of 19 relatives of hæmochromatosis patients (six brothers, five sisters, seven sons and one daughter) were found to show abnormal results for one or more of these three iron-transport values.

TABLE V

Plasma Iron Transport Values for Relatives Showing Abnormal Values

Group	Case Number	Plasma Iron Concentration (µg. per 100 ml.)	Total Iron-Binding Capacity (µg. per 100 ml.)	Percentage Saturation of Iron-Binding Capacity
Brothers ..	6	267	272	98
	16	230	286	80
	17	156	260	60
	17	204	378	54
	19	200	312	64
	21	253	288	88
Sisters ..	7	151	258	59
	7	195	264	74
	11	206	212	97
	16	183	304	60
	23	187	278	67
Sons ..	4	161	270	60
	7	165	269	61
	8	257	304	85
	8	257	296	87
	17	195	304	64
	18	170	265	64
	22	302	330	91
Daughters ..	6	261	286	91

Liver Function Tests

Abnormal values were found in 17 out of the 19 patients on whom liver function tests were performed (Table II). However, in only two relatives, the sisters of Patients 12 and 21, were the liver function test results abnormal. In

both these instances the plasma albumin content was diminished (3·2 and 3·4 gm. per 100 ml.) and the plasma globulin content increased (4·5 and 3·9 gm. per 100 ml.), and in one the plasma alkaline phosphatase content was increased (17·7 King-Armstrong units). Neither of these subjects showed any abnormality of the iron-transport values.

DISCUSSION

Statistically significant differences between means of the iron-transport values of patients' relatives and controls were demonstrable only in the case of the percentage saturation of the iron-binding capacity for sisters and for female controls. However, the total incidence (27%) of abnormal values for individual relatives was much higher than would be expected in a normal population. Abnormal plasma iron and percentage saturation values were found in a total of 38% of male and female siblings and of male offspring of the patients (six out of 13 brothers, five out of 16 sisters and seven out of 18 sons). Although these results cannot prove the mode of inheritance, they are at least compatible with inheritance of an abnormality of iron metabolism by a dominant non-sex-linked gene. Elevation of plasma iron and percentage saturation levels is not specific for hæmochromatosis, but in the relatives of patients with this disease has been considered to be an indication of the presence of the underlying metabolic error (Debré *et alii*, 1958; Bothwell *et alii*, 1959). Elevation of the plasma iron and percentage saturation levels is found, apart from hæmochromatosis, only in transfusional hæmosiderosis, aplastic, hæmolytic and megaloblastic, and in infective hepatitis (Laurell, 1952). Hence the finding of these changes in the iron-transport values in relatives of hæmochromatosis patients in the absence of anæmia or a history of having received blood transfusions probably demonstrates the possession of the defect of iron metabolism occurring in this disease. That such a conclusion is justified is shown by the results of Bothwell *et alii* (1959). He found that of 52 immediate relatives of six patients with idiopathic hæmochromatosis, 11 had elevated serum iron levels. By clinical examination and liver biopsy, three of these relatives were found to have the fully developed disease. In the present investigation clinical examinations or liver biopsies were not performed on the relatives examined. However, two relatives (a brother of Patient 21 and a son of Patient 8) were found to have increased skin pigmentation, and stated that their own doctors had noted liver enlargement. One of these subjects (son of Patient 8) also had diabetes mellitus. Further investigation may disclose that they both have hæmochromatosis.

The lower incidence of abnormal plasma iron values in the daughters (one out of 23 subjects) than in the other relatives examined is a finding similar to that made by Debré *et alii* (1958). They found many abnormal values for sons, and for sons over the age of 15 years could demonstrate that the mean plasma iron concentration was significantly higher than that of the controls, but no such elevation could be demonstrated for daughters. The explanation they gave for this sex difference was that elevation of plasma iron concentration occurs when the iron stores have increased to a certain level owing to increased absorption, and owing to menstrual blood loss this level is reached at a considerably later age in females than in males. This is the reason usually advanced for the sex difference in the incidence of hæmochromatosis. All the daughters examined by Debré and his colleagues and all but three of the daughters examined in the present investigation were aged under 45 years. However, the results of the present work show that in older female relatives (sisters) a high incidence of abnormal plasma iron results may be found. The ages of the six sisters with abnormal results were 58 to 64 years. These observations suggest that the explanation presented by Debré *et alii* to explain the sex difference they found was probably correct.

The demonstration of a high plasma iron concentration in a relative of a patient with idiopathic hæmochromatosis probably means that he has increased storage iron. This is true whether or not there is other evidence of the disease. Finch *et alii* (1950) by bone-marrow biopsy, and Pirart and Gatez (1954) and Bothwell *et alii* (1959) by liver biopsy, have been able to demonstrate increased stainable iron in such relatives in the absence of liver cirrhosis. However, this is not always the case. Bothwell found three relatives of his patients to have elevated serum iron levels, but no increase in stainable iron in the liver. That their stores were not increased, owing to loading with non-stainable iron, was indicated by the early development of iron depletion when venesections were performed. Finch and Finch (1955) considered that the liver and pancreatic fibroses found in hæmochromatosis were the direct result of excessive storage iron deposition. Although this is unproven, it is, however, well known that on removal of the excess storage iron by repeated venesections the patients show clinical and biochemical improvement.

In the present state of our knowledge, then, it would seem justifiable to advise even asymptomatic relatives of patients who have elevated plasma iron values to undergo venesections. The response of the blood hæmoglobin and the plasma iron and iron-binding capacity levels to such treatment would indicate whether or not the iron stores were indeed increased and how often venesections should be repeated. The removal of the excess storage iron may prevent the occurrence of the tissue damage found in the fully-developed disease. Bothwell *et alii* (1959) advocate such an approach to this problem.

Although the tests of liver function used in this investigation must be considered rather insensitive, the observation that no abnormal results were found in relatives with elevated plasma iron levels is of significance. The results suggest that the plasma iron concentration is a much more delicate way of detecting affected individuals than are the liver function tests. The results also suggest that the alterations of iron metabolism precede the development of liver damage, and may indeed cause the damage, as has been postulated by Finch and Finch (1955). The significance of the abnormal liver function found in the sisters of Patients 13 and 31, in the presence of normal plasma iron values, is uncertain. It is not known whether the results indicate liver disease, and if so, whether this is due to the inherited defect of hæmochromatosis or whether it is due to some other cause. If the abnormalities are due to hæmochromatosis, it would appear that rarely evidence of altered liver function precedes that of altered iron metabolism.

Although there is considerable evidence as to the inherited nature of the majority of cases of idiopathic hæmochromatosis, it is still uncertain whether all cases given this diagnosis have a genetic ætiology. The high incidence of alcoholism found in any series of cases of hæmochromatosis (Sheldon, 1935; Finch and Finch, 1955) indicates that environmental factors may play a part in the development of the disease. Two recent papers (Tuttle *et alii*, 1959; Houffbauer, 1960) have described cases in which hepatic cirrhosis was diagnosed by liver biopsy, there being little stainable iron in the livers at these times, and then, a short while later at death, the histological picture of the liver was that of hæmochromatosis. Were these cases of inherited idiopathic hæmochromatosis in which the cirrhosis preceded the excessive deposition of storage iron? Or were they cases of cirrhosis due to other causes, with increased iron absorption and storage as a late change in the natural history of the disease, the resulting histological appearance of the liver being indistinguishable from that of the inherited form of hæmochromatosis?

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PRELIMINARY STUDY OF FAMILY WITH HEREDITARY HYPERCHOLESTEROLÆMIC XANTHOMATOSIS[1]

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SUMMARY

A study has been made of 79 members comprising three generations of a family affected by hereditary idiopathic hypercholesterolæmia. Eighteen of 64 living members were found to have hypercholesterolæmia, and the distribution suggested a dominant trait type of inheritance. All the lesions traditionally associated with the hypercholesterolæmic state were found in members of this family, but only peripheral skin and tendon xanthomas showed a definite relationship to serum cholesterol level. Arcus senilis and xanthelasma palpebrarum occurred in individuals with normal serum cholesterol levels as well as in hypercholesterolæmic subjects. Three adults with hypercholesterolæmia showed none of the external signs. These lesions developed in no fixed sequence, and time relationships were extremely variable in hypercholesterolæmic individuals as well as in those with normal serum cholesterol levels. It was concluded that the serum cholesterol level might not be the critical factor in the development of these lesions. A high incidence of coronary artery disease correlated well with the hypercholesterolæmic state, but not with external signs. In this family hypercholesterolæmia was not associated with hyperuricæmia.

THE LIPOIDOSES

THE lipoidoses form a complex group of disorders in which the basic metabolic disturbances involved are still unknown. From the time of Addision and Gull, many clinical descriptions of " xanthomatous " disorders have been recorded in the literature. These clinical descriptions present a confusing picture when considered together. Thannhauser (1958) brought some order into this confusion by tabulating three broad groups of disorders, having in common the presence in various tissues of collections of lipid and cholesterol, termed xanthomas.

(1) Idiopathic hypercholesterolæmic xanthomatosis is a familial disorder in which xanthomatous deposits of pure cholesterol and cholesterol esters accumulate in the skin, tendons and deeper tissues. The serum cholesterol level is elevated, the serum itself remaining clear with only slight elevation of neutral fat content. Relatives of affected individuals may have hypercholesterolæmia without xanthomas. There is a high incidence of degenerative vascular disease in these families.

(2) The lipoid granuloma group is also familial. It includes the Hand-Schüller-Christian disorder, in which serum cholesterol and fatty acid ester levels are normal. Xanthomas occur in spleen, liver, brain, bone, lungs, pleura, lymph nodes and skin, and consist of intracellular deposits of phospholipids.

(3) The hyperlipæmias, with secondary xanthomatosis, are characterized by xanthomas in the skin and often on flexor surfaces, mucosal lesions and a milky serum with high serum fatty acid ester content. The condition is not necessarily familial, and lesions can be reversed by diet to a considerable degree.

The boundaries between these three broad groups are not always clearly defined. The current interest in cholesterol and lipid metabolism in relation to vascular diseases has led to an increased interest in the lipoidoses, and has focused attention on the inadequacy of many of the data available concerning the clinical associations of high serum cholesterol levels.

This paper describes a preliminary survey of a family known to contain individuals with hypercholesterolæmic xanthomatosis, conforming most closely to Group I of Thannhauser's classification. Particular attention has been paid to (i) the incidence of hypercholesterolæmia in asymptomatic relatives, (ii) the order and age of appearance of signs of the condition in relation to the hypercholesterolæmic state, (iii) the mode of inheritance, and (iv) the question of association with hyperuricæmia.

METHOD OF STUDY

Details of the family tree were obtained from members of the family, from old hospital case notes, from autopsy reports on two members,

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and from private doctors' records. Members of the family were examined in most instances by one person. Symptoms of cardio-vascular diseases, gout, diabetes, or biliary or pancreatic disease were noted. The times of appearance of skin and tendon lesions were recorded, and a careful search was made for arcus senilis and for skin, tendon and mucosal lesions. In addition, the precordium was examined, the blood pressure was measured and the peripheral pulses were examined. The biochemical determinations were made in one laboratory in all but four cases. Serum cholesterol levels were estimated by the method of Sackett (1925), serum uric acid levels as described by King and Wooton (1951), and serum fatty acid ester levels by the method of Stern and Shapiro (1953).

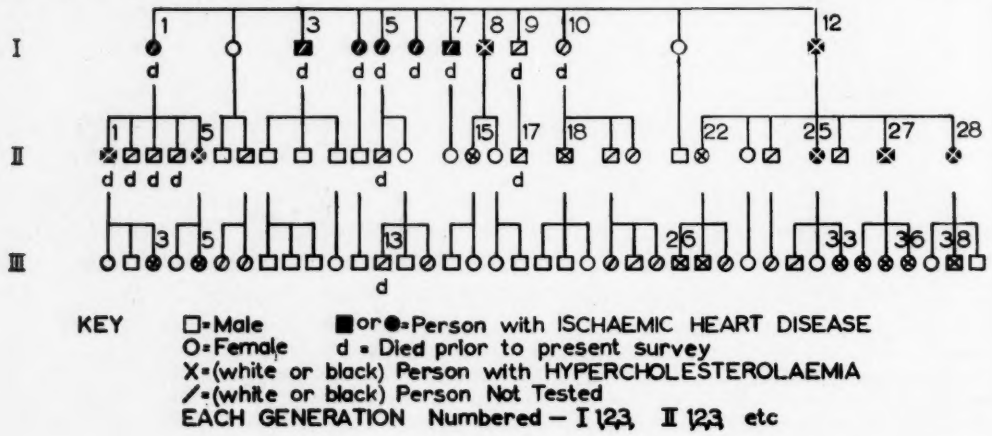

FIGURE I

Idiopathic familial hypercholesterolæmia. Three-generation pedigree of family

Normal serum cholesterol levels for the Auckland population by the method used have a range of 120 to 240 mg. per 100 ml., a much lower value than that usually recorded (see Appendix I). A person was arbitrarily regarded as having hypercholesterolæmia if the serum cholesterol level was above 270 mg. over the age of 20 years, and above 250 mg. in childhood. The uric acid level range for normal subjects in this laboratory was 1·5 to 6·0 mg. per 100 ml., and the serum fatty acid ester range of normality was 2 to 14 mEq/l.

RESULTS

Family Tree

Of 79 individuals in the three generations studied, 64 were alive at the time of the survey, and 50 (78%) of the latter were examined fully. Incomplete information was obtained on all the remaining 14 living members. Of the 15 individuals no longer alive, four had died in infancy, complete information was available on one, and fair clinical detail was available on another six members. A further death (No. II 5) has occurred since the survey was completed.

Biochemical Data

Blood for biochemical examination was obtained from 50 individuals.

Serum Cholesterol Levels.—Eighteen members were found to have hypercholesterolæmia by the criteria listed above (Table IB). The range was 260 to 690 mg. per 100 ml. A further member, who had died a few months before the survey began, had had a cholesterol level of 565 mg. per 100 ml. (mean value). This man and six of the living members had had serial cholesterol determinations.

Serum Fatty Acid Ester Levels.—Values for the 18 living hypercholesterolæmic members ranged from 9·3 to 39·5 mEq/l., with a mean value of 21·3 (Table IB). Of these 18 members, only seven children had fatty acid ester levels within the normal range. The 32 persons with normal blood cholesterol levels had fatty acid ester levels ranging from 3·9 to 18·9 mEq/l., with a mean of 14·6.

Blood Uric Acid Levels.—The range for the 18 hypercholesterolæmic subjects was 2·2 to 5·8 mg. per 100 ml., with a mean value of 3·3. For the 33 normocholesterolæmic members, the range was 1·7 to 6·0, with a mean value of 3·4.

Clinical Findings

Incidence of Coronary Artery Disease.—The details relating to coronary artery disease are

set out in Tables IA and IB. In these three generations there have been 16 deaths, including the female member No. II 5. Of these deaths, four occurred in infancy, two were battle casualties, and one man, aged 18 years, died from tuberculosis.—One woman died, aged 79 years, from complications of diabetes. The remaining eight deceased members included five women aged 36, 50, 54, 60 and 60 years respectively, in whom the major factor leading to death was coronary artery disease. Three men, aged 52, 65 and 66 years, have died from myocardial infarctions. One man and one woman who died were known to have had gross elevation of the serum cholesterol level.

Of the 64 living members, two women, aged 34 and 32 years, had symptoms of coronary insufficiency, and so had two men, aged 65 and 66 years. These four living subjects all had hypercholesterolæmia.

TABLE IA

Details of Five Members of Family who Died before the Present Survey was Begun

Serial Number in Pedigree, Table I	Sex	Age in Years at Death	Cardio-vascular Status	Arcus Senilis	Xanthelasma; Palpebrarum	Xanthomas of Skin and Tendon	Blood Cholesterol Level (mg. per 100 ml.)	Serum Fatty Acid Content (mEq)	Blood Uric Acid Level (mg. per 100 ml.)	Arthritic Symptoms
I 6	F.	36	Angina of effort; sudden death in sleep	No data	Present	Present	—	—	—	No data
I 5	F.	50	Angina; died of "heart attack"	No data	No data	No data	—	—	—	No data
II 1	M.	52	Died of myocardial infarction	Absent	Present	Present	565[1]	39·4	4·1	Present
I 1	F.	60	Died of "heart attack"	No data	Present	Present	—	—	—	No data
I 4	F.	60	Died of "heart attack"	No data	Present	Present	—	—	—	No data

[1] Mean of six values over five years.

TABLE IB

Details of 18 Members of Family with Hypercholesterolæmia Alive at Time of Present Survey

Serial Number in Pedigree, Table I	Sex	Age (Years)	Symptoms and Signs of Coronary Insufficiency	Arcus Senilis	Xanthelasma Palpebrarum	Xanthomas of Skin and Tendons	Blood Cholesterol Content (mg. per 100 ml.)[1]	Serum Fatty Acid Ester Content (mEq/l.)	Blood Uric Acid Content (mg. per 100 ml.)	Arthritic Symptoms
III 34	F.	3					234	16·2	2·7	
III 38	M.	3					268	9·3	4·2	
III 33	F.	4					272	16·4	2·7	
III 35	F.	5					308	17·3	2·6	
III 36	F.	7					282	13·4	2·9	
III 27	M.	6					268	12·3	2·4	
III 26	M.	10					272	16·0	2·0	
III 3	F.	14				+	348	15·4	2·6	Metatarso - phalangeal joints
III 5	F.	16		+		+	440	26·2	5·8	
II 22	F.	27					294	25·3	3·0	
II 27	M.	28	+	+		+	370	39·8	5·4	
II 25	F.	32	+				284	15·8	3·2	
II 28	F.	34				+	365	25·2	3·0	
II 15	F.	35					324	19·0	2·3	
II 18	M.	42		+			304	17·6	4·3	
II 5	F.	54	+	+	+	+	690	30·9	2·8	Metatarso - phalangeal joints
I 8	M.	65	+	+			272	25·3	2·2	
I 12	M.	66	+		+		288	23·3	5·2	

[1] For discussion of normal range see Appendix.

Incidence of Xanthomas.—The incidence of xanthomas is set out in Table II.

(1) Xanthelasma palpebrarum. These were seen typically as plaques on the upper eyelids. Five living persons, including two with hypercholesterolæmia, showed these lesions. Four dead members were known to have had xanthelasma.

(2) Xanthomas of skin. Plane and tuberose forms were seen, typically on extensor surfaces and at sites where friction was common (Figure IV). Four living persons showed these lesions (Table II), and four dead patients were known to have had skin xanthomas. The earliest age at which a skin deposit had been observed was in a girl, aged 11 years; two further subjects had developed skin lesions in their early teens.

(3) Xanthomas of tendons. These took the form of deposits in the tendons themselves (Figures II and III), obvious externally as knobbly lumps elevating the skin over the lines of the affected tendons (Figures IV and V). In one girl, deposits in the tendo Achillis were first noted at the age of 11 years. In one male patient with hypercholesterolæmia, no tendon deposits were obvious until the age of 25 years. No cases of skin or tendon xanthoma were seen in normocholesterolæmic members of the family.

(4) Xanthomatous deposits in deeper tissues. At the only two autopsies in the series, xanthomatous deposits were noted in relation to deep fascia, as opposed to subcutaneous tissues. Patient No. 13 had deposits in the mesentery, on valve cusps and on chordæ tendineæ. A further patient had been noted to have xanthomatous deposits in his mesentery at the time of resection for colonic carcinoma. Deposits were present in the pulmonary arteries of both patients subjected to autopsy.

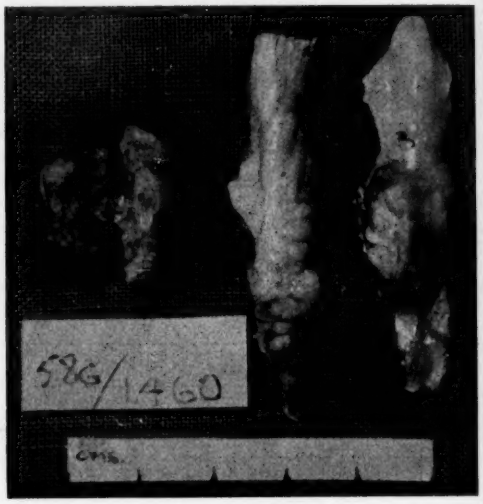

FIGURE II

Autopsy specimen showing xanthomatous deposits in the substance of extensor communis digitorum tendons

(5) Mucosal lesions. No deposits were seen in any of the patients examined, and none were noted at either autopsy.

TABLE II

Distribution of Arcus Senilis, Xanthelasma Palpebrarum and Xanthomas of Skin and Tendons in Persons with Normal and Elevated Serum Cholesterol Levels, Correlated with Age and Incidence of Coronary Artery Disease

External Sign or Combination of Signs	Age (Years) at Time of Survey	Age (Years) at Time of Appearance of Lesion First Mentioned	Serum Cholesterol Level (mg. per 100 ml.)	Sex	Evidence of Coronary Artery Disease	Number in Pedigree, Table I
Arcus senilis alone	29	?	230	F.		II 16
	42	?	304[2]	M.		II 18
	46	?	210	M.		II 11
	61	?	215	F.		I 2
	65	? 40	275[2]	M.	+	I 8
Arcus and xanthelasma palpebrarum	49	? 30	222	F.		II 14
Arcus and xanthomas of skin and tendons	16	12	440[2]	F.		III 5
	28	?	370[2]	M.	+	II 27
	54[1]	30	690[2]	F.	+	II 5
Xanthelasma palpebrarum alone	21	16	180	F.		III 1
	26	?	225	F.		III 4
	66	?	288[2]	M.	+	I 12
Xanthelasma palpebrarum and xanthomas of skin and tendon	52[1]	47	565[2]	M.	+	II 1
	54[1]	20	690[2]	F.	+	II 5
Xanthomas of skin and tendon alone	14	11	348[2]	F.		III 3
	34	30	365[2]	F.		II 28
Xanthomas of skin and tendon with arcus senilis	16	12	440[2]	F.		III 5
Xanthomas of skin and tendon and xanthelasma palpebrarum	28	?	370[2]	M.	+	II 27
	52[1]	25	565[2]	M.	+	II 1
Xanthomas of skin and tendon with arcus senilis and xanthelasma palpebrarum	54[1]	16	690[2]	F.	+	II 5

[1] Age at death.
[2] Hypercholesterolæmic subject.

Arcus Senilis.—Of 64 living members, nine had an arcus, and five of these persons had hypercholesterolæmia (Table II). Of those with hypercholesterolæmia, five young children and six other patients, aged respectively 14, 27, 32, 34, 35 and 66 years, had no arcus.

Hypercholesterolæmia Without Signs.—Of 19 known members with hypercholesterolæmia (18 living and one dead), 10 persons showed none of the above-mentioned signs; but of these 10, seven were children. The three asymptomatic adults were all women, aged 27, 32 and 35 years respectively, with blood cholesterol levels ranging between 284 and 324 mg. per 100 ml.

Other Clinical Associations.—There was one doubtful case of biliary colic in the series, and there were no cases of pancreatitis. Two cases of mild diabetes were encountered in overweight middle-aged men. One woman had died at the age of 70 years of diabetes, which developed in late middle life and required insulin for control. Casual blood glucose levels were determined in the overweight members of the family, and these were all within normal limits. Body weight bore no correlation to the presence of hypercholesterolæmia in this series. Pregnancy did not obviously increase the rate of accumulation of external xanthomas in two women with hypercholesterolæmia.

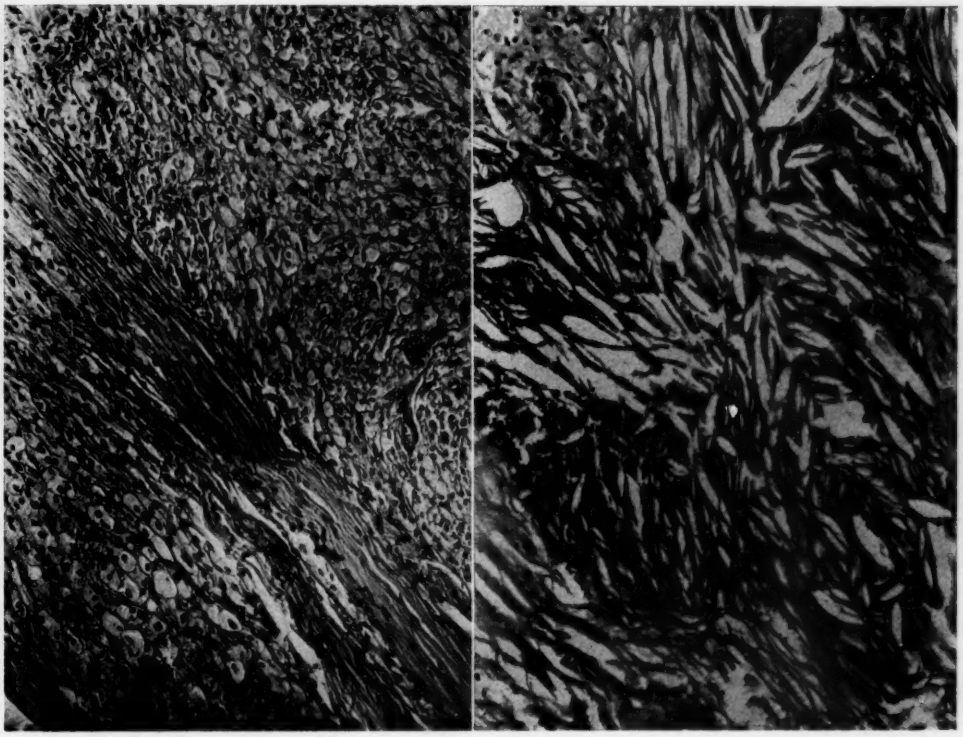

FIGURE III

Photomicrographs showing histology of tendon xanthomas. The xanthoma cells with foamy cholesterol-filled cytoplasm disrupt the tendon fibres. The high-power view shows cholesterol clefts in the same specimen

DISCUSSION

Although the numbers are limited, certain interesting points have emerged from the preliminary study of this family.

The present intensive study of cholesterol and lipid metabolism has not yet assigned a definite place to cholesterol in any pathological cycle of events; nor is it certain that disturbance of cholesterol or lipid metabolism is a primary event in the course of vascular degenerative diseases. The present study would indicate that mere elevation of blood cholesterol level is not the determining factor in the appearance of external lesions, such as xanthelasma,

regarded as typical of the hypercholesterolæmic state. Thus six individuals with normal blood cholesterol levels had xanthelasma or arcus senilis, while three members with hypercholesterolæmia over the age of 25 years had none of these classical signs (Piper *et alii*, 1956; Leonard, 1956). It was concluded that there was no critical serum cholesterol level at which signs appeared in this family. This feature, together with an absence of a definite sequence of events in the case histories of hypercholesterolæmic individuals, would suggest that, in this family, the basic metabolic fault was more than a simple derangement of blood cholesterol level. It is not surprising, in view of this lack of critical blood cholesterol level,

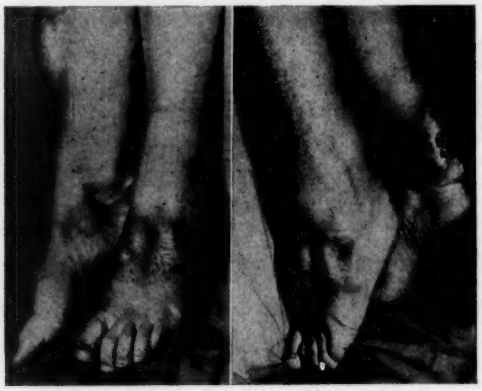

FIGURE IV
Showing gross xanthomas of lower limbs in patient with idiopathic hypercholesterolæmia

that dietary and other measures, which partially lower blood cholesterol and lipid levels, should fail to affect established peripheral and vascular lesions and also prove disappointing in their effect on the clinical course of the disease (Leonard, 1956).

The prognosis in this condition is determined by the incidence of coronary artery involvement. Much has been written in the past concerning the order of appearance of various external xanthomatous deposits, in an attempt to relate the time of appearance and extent of such lesions to the degree of cardio-vascular degeneration in a given individual. In this pedigree, arcus senilis, xanthoma palpebrarum and xanthomas of skin and tendon were all encountered in varying age groups, singly and in varying combinations in both normal and hypercholesterolæmic individuals (Tables IA and IB). No one lesion was more common in any age group (Piper, 1956). Arcus senilis and xanthelasma palpebrarum in particular showed little correlation with blood cholesterol levels. The presence of xanthomatous deposits in the skin and tendons did bear a much closer relationship to cardio-vascular signs; but there was no overall correlation between the progressive development of such lesions and vascular disease. Thus Patient II 1 developed intermittent claudication at the age of 18 years, and developed minor xanthomas in later life. His sister

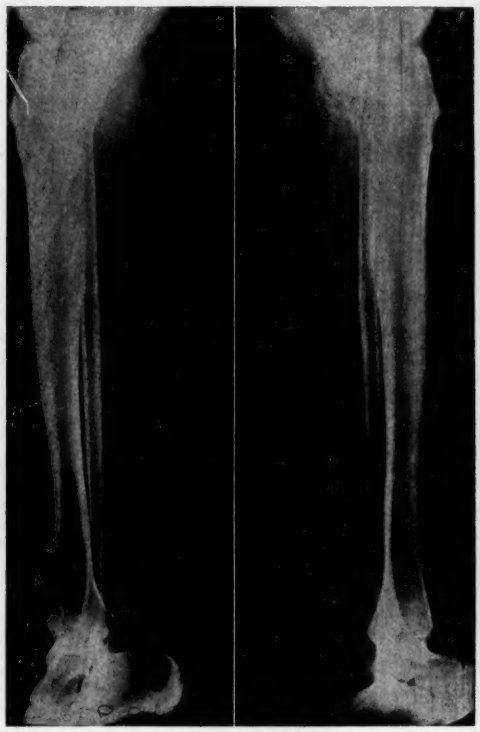

FIGURE V
Lateral radiographs of legs show soft-tissue masses with erosion of tibial tuberosities and anterior surface of right tibia in relation to large deposits in skin and subcutaneous tissues

developed massive xanthomas at the age of 16 years, and did not suffer symptoms from ultimately fatal coronary artery disease till the age of 50 years. Moreover, three patients with hypercholesterolæmia and coronary artery disease had no external xanthomas. Although external xanthomas showed no correlation with the presence or extent of atheroma, yet it was noted that, without exception, patients with coronary artery disease had blood cholesterol levels above the upper limit of normal. In all, six members with ischæmic heart disease were found to have hypercholesterolæmia. Included

in Appendix I are a series of figures for cholesterol values of unrelated cases of myocardial infarction from the same hospital laboratory, showing again a mean blood cholesterol level above that of the general population.

The known high incidence of coronary artery disease in families with idiopathic hypercholesterolæmic xanthomatosis was confirmed, particularly among women. Piper (1956) suggests a different type of coronary lesion in such patients and the rate of progression of cardiac signs and symptoms in the family, reflected in the age of death from coronary artery disease, seems more rapid than is the usual case among atheromatous subjects in the general population. Certainly hypercholesterolæmia and membership of a family such as this carries a poor prognosis (Tables IA and IB). While they bear no direct relationship to vascular lesions, arcus, xanthelasma and xanthomas of skin and tendon occur sufficiently commonly in hypercholesterolæmic individuals to require an estimation of blood cholesterol content whenever they are noted. At the same time, a poor prognosis need not be considered inevitable if the blood cholesterol level so obtained is normal.

Both patients who came to autopsy had atheromatous deposits in the pulmonary artery. One of these, a male, aged 52 years, had aortic incompetence, and xanthomatous deposits were found in the aortic valve and chordæ tendineæ. His sister had an aortic systolic murmur, and at autopsy a calcified aortic valve was found.

There is a preponderance of two females to one male person among the hypercholesterolæmic individuals in this series. However, this may not be significant, in view of the fact that three neonatal deaths in males occurred in the most heavily affected branch of the family. There was no significant difference between the ages of death for men and women.

The mode of inheritance of this disorder has been disputed in the past, and the literature on this point is confusing. Wilkinson *et alii* (1948) suggested inheritance of an incomplete dominant trait, with xanthomatosis the homozygous form and essential hypercholesterolæmia without xanthomatosis the heterozygous form. However, Harris Jones *et alii* (1957) described a patient with idiopathic hypercholesterolæmic xanthomatosis, who had a parent and a son with normal cholesterol levels. They suggested a dominant trait pattern of inheritance. Piper and Orrild (1956) agreed with this, and Leonard's (1956) results were consistent with this view. A dominant trait best fits the pattern in the present family. In this preliminary survey, the blood cholesterol levels of spouses of subjects were not determined. It is known that the spouses of two members with hypercholesterolæmia and affected children had normal serum cholesterol levels.

The serum fatty acid ester level in this series is a little higher than in some reported series of pure idiopathic hypercholesterolæmic xanthomatosis (Thannhauser, 1958; Adlersberg, 1955; Koch *et alii*, 1956; Malmros *et alii*, 1954; Borrie, 1957), but the authors quoted above all mention mixed forms of the disorder. There was good correlation between elevation of the serum fatty acid ester level and the serum cholesterol level (Table II).

Adlersberg (1951) was among the first to stress a possible relationship between this condition and gout. More recently, it has been stated (Harris Jones, 1957) that the blood uric acid level is often elevated in members of these families. Both gout and hypercholesterolæmia have an association with coronary artery disease (Gertler *et alii*, 1951). Only three members of the present family admitted to joint symptoms of any consequence. All three showed no abnormalities on X-ray examination of their small joints. Two of these were children with normal serum uric acid levels. Their father suffered from pains in the small joints of his feet. His serum uric acid level was at high normal figures; colchicine and salicylates did relieve his pain. X-ray films of the feet of Patient II 5 showed punched-out areas in the distal phalanges of several toes. Unfortunately these were not investigated at autopsy (Koch *et alii*, 1956).

The suggestion of Gofman *et alii* (1954) that xanthoma of tendons and xanthoma tuberosum of skin develop in different age groups and may be based on different biochemical disorders, received no clinical support from study of this particular family, in that skin and tendon lesions appeared together at varying ages and in varying patterns.

There was no increased incidence of biliary tract disorders or of pancreatitis.

It was hoped that this preliminary survey would reveal the children and adolescents likely to develop cardio-vascular complications in later life. It is probable that most of these individuals have been discovered, and they will be followed further with the hope that successful prophylaxis may be possible. At present no preventive measures of proven value are available to help these people. As has been indicated above, it may yet be shown that the elevation of blood cholesterol level is not the primary defect, and that successful lowering of the blood cholesterol level will not prevent the development of this disorder. Nevertheless it seems prudent, even in the present state of uncertainty,

to offer dietary measures and drugs to these people, in an attempt to lower the blood cholesterol level. Diets of low fat and cholesterol contents (Breslau, 1958), thyroid (Breslau, 1958), nicotinic acid (Leonard, 1956), unsaturated fatty acids (Bronte-Stewart *et alii*, 1956; Malmros, 1954) and inhibitors of cholesterol biosynthesis have all been advocated. No single measure or combination at present available appears to lower the blood cholesterol level invariably or permanently.

ACKNOWLEDGEMENTS

I wish to thank Professor E. G. Sayers, Dr. F. H. Sims and Dr. H. K. Ibbertson for help in conducting the investigation. This study was made possible by the staff of the Central Laboratory, Auckland, who carried out the biochemical estimations, and by the many doctors who provided case notes and helped us to meet members of this family. The autopsies were performed by Dr. F. Smith and Dr. J. Sullivan. I wish to thank Mrs. Craven, Miss L. Browne and Miss M. Bailey for secretarial assistance. I am grateful to Mr. H. S. Kendrick, superintendent-in-chief of the Auckland Hospital Board, for permission to publish this paper. The investigation would not have been possible without the excellent cooperation given by members of the family.

APPENDIX I

No adequate control series was available to show the normal range of serum cholesterol values for the method used in the survey. Accordingly, an initially unselected six-months series of blood cholesterol levels from hospital in-patients was checked against the case notes. Cases of nephrosis, myxœdema, diabetes, lipoidoses and proven coronary artery disease were excluded. The remaining subjects had had serum cholesterol estimations made for a variety of reasons. No sex difference was found in the range or mean, and the figures were combined with the following results.

Patients aged 2 to 40 years numbered 54; their mean value was 184·9 mg. per 100 ml., the range was 125 to 255 mg. per 100 ml., and the standard deviation was 26·2 mg. per 100 ml.

Patients aged 40 to 80 years numbered 64; their mean value was 194·3 mg. per 100 ml., the range was 135 to 240 mg. per 100 ml., and the standard deviation was 28·2 mg. per 100 ml.

A group of male patients with myocardial infarctions, aged 31 to 70 years, gave the following figures: mean, 215·6 mg. per 100 ml.; range, 165 to 295 mg. per 100 ml.; standard deviation, 30·3 mg. per 100 ml.

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THE ASSOCIATION OF LUNG CANCER AND TUBERCULOSIS[1]

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SUMMARY

As part of an investigation of the relationship between pulmonary tuberculosis and lung cancer, 6502 ex-servicemen with tuberculosis were reviewed during various periods in three Australian States for a total of 25,827 " man-years ". The number of deaths from various causes was compared with the number of expected deaths calculated from the age-specific mortality rates of each disease classification in each of the three States.

The tuberculous group had an excess mortality from certain chest conditions (59 actual deaths, 29 expected, $P=0{\cdot}00008$), from certain heart diseases (85 observed deaths, 44 expected, $P=0{\cdot}00001$) and from lung cancer (34 actual deaths, 13 expected, $P=0{\cdot}0005$). The excess deaths from lung cancer were spread proportionately throughout the usual age groups. In the majority, tuberculosis had been inactive for at least a year prior to the first appearance of the lung cancer.

Fourteen of the 24 patients with lung cancer in Victoria and Queensland had available adequate X-ray films prior to the development of the lung cancer. The maximum involvement of tuberculosis and the site of the lung cancer were charted according to the lung zones involved. Lung cancer arose more frequently in the 38 involved zones (11 cases) than in the 46 uninvolved zones (3 cases). The difference was significant ($0{\cdot}02>P>0{\cdot}01$).

After consideration of other likely explanations, it is possible to suggest that pulmonary tuberculosis has a causal effect on lung cancer, and this effect may be through such non-specific changes as scarring or metaplasia of the bronchial mucosa.

THE possibility of a relationship between tuberculosis and cancer has attracted investigation and speculation for many years.

Recently, Schwartz (1956) reviewed the many reports of an association between pulmonary tuberculosis and lung cancer, and described benign and malignant tumours arising at the site of long-standing tuberculous bronchial scars produced by perforations from tuberculous lymph nodes. Such scars were usually covered by metaplastic squamous epithelium. Amongst the cases described were 13 malignant tumours apparently arising from a bronchial scar.

In an important investigation, Gelzer (1956) reviewed the autopsy findings in 539 cases of lung cancer. There were 80 (13%) peripherally located lung cancers; 35 (43·7%) originated in scar tissue. The originating scar tissue was tuberculous in 79·5%, and 78% of the peripheral cancers occurred in the upper lobes. Burgel and Themel (1958) have confirmed that the so-called scar cancer develops mostly from healed tuberculous lesions (33 out of 37 cases). Twenty-six of the cancers were accordingly located in the upper lobes. From a series of operation and autopsy cases, Walter and Pryce (1955) produced evidence that more than 50% of lung cancers are initially peripheral, and that 55% of these show central pigmented scarring.

Finke (1956), in a study of a series of lung cancer cases, found chronic lung disease (chronic bronchitis, asthma and tuberculosis) in 70% of cases.

Although the reports of the association of the two diseases at the same site suggest the possibility of a relationship between tuberculosis and lung cancer, it has yet to be determined how frequently such an association would be due to coincidence.

Carey and Greer (1958) reviewed the English language literature, and analysed the clinical reports of 148 patients with both lung cancer and tuberculosis. Although they attempted to assess the frequency with which the two diseases were closely associated, many of the original case reports were admittedly incomplete, so that their failure to demonstrate a close association is of doubtful authenticity. Moreover, Oudet and Rougel (1958) found that in 13 cases of tuberculosis definitely preceding carcinoma of the lung, the cancer was related topographically to the tuberculosis in 11 cases.

In contrast to the pathological and clinical observations, epidemiological surveys by Doll

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and Hill (1952) and by Denoix *et alii* (1958) failed to show any relationship between pulmonary tuberculosis and lung cancer. As part of larger investigations into the cause of lung cancer, they examined the incidence of pulmonary tuberculosis amongst patients with lung cancer; compared with controls, the incidence of tuberculosis was not more frequent in persons with lung cancer. On first examination, this work appears to provide strong evidence against a relationship between tuberculosis and cancer. However, the possibility of some degree of intrinsic selection cannot be fully excluded in these investigations, as both groups of authors obtained their material from hospitals other than those dealing solely with tuberculosis. Owing to the practice of treating patients with tuberculosis in special institutions, inevitably some remain in these institutions after a pulmonary neoplasm becomes apparent. As a result, the number of lung cancer patients with tuberculosis in general hospitals is likely to provide an under-estimation of the true incidence of tuberculosis in patients with lung cancer.

Owing to the low percentage of persons with tuberculosis in the population, a small reduction of the number of lung cancer patients with tuberculosis would be of crucial importance and could readily bias the results adversely.

In general, although the pathological and clinical studies suggest a relationship, the previous studies have been incomplete, and the results have been contradictory. The present investigation includes an epidemiological study of the frequency with which malignant neoplasms develop in persons with pulmonary tuberculosis, and an investigation into the frequency with which lung cancer develops at the site of prior tuberculosis.

The Occurrence of Malignant Neoplasms in Persons Sometime Diagnosed as Tuberculous

Methods and Materials

The Repatriation Department maintains contact during life with all ex-servicemen diagnosed as being tuberculous. All patients in Queensland, Victoria and Western Australia (three of the six Australian States) have been studied over specified periods of time, and the mortality experience has been compared with that of the male population of the State concerned.

The first group consists of all male ex-servicemen with tuberculosis living in the State of Queensland on January 1, 1949, together with all cases diagnosed between January 1, 1949, and December 31, 1958. The second group consists of all ex-servicemen with tuberculosis living in Western Australia on June 30, 1950, together with all cases diagnosed to June 30, 1958. The third group comprises all ex-servicemen with tuberculosis living in Victoria on June 30, 1956, together with all cases diagnosed to June 30, 1959.

Six thousand five hundred and two persons (95·4% with pulmonary and 4·6% with extra-pulmonary tuberculosis) were reviewed during the various periods in the three States for a total of 25,827 " man-years ". There were 858 deaths during the periods of review.

During the review periods, the deaths that occurred amongst the Victorian, Queensland and Western Australian patients were recorded from the death certificates. When malignant disease was recorded as a cause of death, the original clinical records were searched. As a result, the cause of death was revised in several cases.

The " expected " deaths, for each disease classification examined, were calculated from the age-specific mortality rates for each disease classification in each of the three States.

In Queensland, for each of the nine years 1949 to 1958, the tuberculous patients were grouped according to age into five-year age groups. By adding together the number living in each year, the total number of " life-years " was obtained for each age group. When a patient had been diagnosed, had been transferred into or out of the State, or had died during the year, he was recorded as having lived a half a year.

The total number of " life-years " for each age group multiplied by the Queensland male mortality rate for each age group provides the expected number of deaths from various causes. To correspond as closely as possible with the observed period, the Queensland mortality rates were for the years 1950 to 1955 to multiply with the " life-years " between 1949 and 1956, and for the period 1956 to 1957 for the " life-years " 1957 and 1958.

Similar calculations of " expected " deaths were made for Victoria and Western Australia. In Western Australia, the age-specific death rates for the period 1950 to 1957 were averaged. In Victoria, the average age-specific mortality rates for 1957 and 1958 were employed.

In Western Australia, a slight approximation was necessary in calculating the number of expected deaths from the number of tuberculous patients. For each of the eight years, the patients had been placed in groups designated by years of birth. These groups did not necessarily correspond exactly with the statistical five-year

age group. The groups classified according to the year of birth can be readily converted into age groups which in some instances correspond with the statistical five-year age groups, or else are either slightly younger or slightly older. The approximation consisted of allotting each of the "year of birth" groups to the five-year age group which corresponded with the age of the majority in the group. This exaggerated the ages by two to three years in some groups and reduced them to the same extent in others. Therefore, any error introduced by this approximation is likely to be slight and largely self-cancelling.

The significance of differences between the "found" and "expected" deaths has been assessed by the method described by Case and Lea (1955). By using the approximation of regarding the square root of the number of deaths found as the standard error, the *P* value is then determined from tables of the normal curve from the observed difference between the expectation and the number found over the square root of the number found.

Results

The differences between the deaths observed and those expected are very similar in all three of the Australian States; only in neoplasms other than lung cancer and to a lesser extent in heart disease where there local dissimilarities (see Table I). Such relative uniformity in widely separated localities speaks against bias by the investigator and provides a certain confidence in the technique and general results.

Mortality Experience. — The tuberculous patients have an excessive mortality due to tuberculosis, other chest conditions, certain heart conditions and lung cancer. Deaths from other conditions, including coronary heart disease, vascular disease of the central nervous system, violence, non-pulmonary neoplasms and all other causes not dealt with specifically, show no significant difference between the actual and expected deaths.

Mortality from Pulmonary Tuberculosis, Other Chest Conditions and Certain Heart Diseases.— The tuberculous group naturally have an excess mortality from pulmonary tuberculosis, and this requires no further discussion. In addition, there is an excess mortality from chest conditions other than lung cancer and tuberculosis. There were 59 actual deaths and 29 deaths expected, a highly significant difference ($P=0{\cdot}00008$). The chest diseases were chiefly bronchitis, emphysema and pneumonia. Deaths from heart disease other than coronary heart disease are likewise excessive—85 observed deaths compared with 44 expected ($P=0{\cdot}00001$).

Mortality from Neoplasms.—Amongst the persons with tuberculosis, 105 deaths were due to malignant process, 70 deaths were "expected". The difference is highly significant ($P=0{\cdot}0007$).

Mortality from Lung Cancer.—The excess of deaths from all cancer is due chiefly to the excessive death rate from lung cancer. There were 34 actual deaths from lung cancer compared with 13 expected deaths. The difference is highly significant ($P=0{\cdot}0005$).

TABLE I

Actual and Expected Mortality of Tuberculous Males

State	Deaths	Total Malignant Neoplasms	Lung Cancer	All Other Neoplasms	Coronary Heart Disease	All Other Heart Disease	Vascular Disease of the Central Nervous System	Tuberculosis of the Lungs	All Other Respiratory Disease	Violence, etc.	All Other Cases	All Causes
Queensland	Actual	27	12	15	62	52	21	167	25	11	32	397
	Expected	29·71	4·69	25·02	43·77	20·18	21·01	4·33	11·46	13·53	43·28	187·27
Western Australia ..	Actual	35	10	25	24	20	13	85	14	5	22	218
	Expected	13·94	3·11	10·83	23·66	12·45	9·11	1·84	6·44	9·46	21·15	98·05
Victoria ..	Actual	43	12	31	42	13	21	68	20	10	26	243
	Expected	26·31	5·68	20·63	43·53	11·81	16·13	1·42	10·64	10·66	29·91	150·41
Total ..	Actual	105	34	71	128	85	55	320	59	26	80	858
	Expected	69·96	13·48	56·48	110·96	44·54	46·25	7·59	28·54	33·65	94·34	435·73
		$P=$ <0·0007	$P=$ 0·0005	$P=$ 0·09	$P=$ 0·11	$P=$ 0·00001	$P=$ 0·24	$P=$ <0·0000001	$P=$ 0·00008	$P=$ 0·13	$P=$ 0·11	
		Significant	Significant	Not significant	Not significant	Significant	Not significant	Significant	Significant	Not significant	Not significant	

Age at Death from Lung Cancer.—The 24 deaths from lung cancer in Queensland and Victoria have been classified according to age at death and compared with expected deaths for various age groups.

Table II shows an excess of deaths in the various age groups. The numbers are small, but the spread of excess of deaths throughout the various age groups shows that there has been no tendency for lung cancer to occur at an earlier age than usual. Of the deaths under the age of 60 years, the number observed was 2·5 times the expected number. Similarly, 2·3 times the expected number of subjects died after the age of 60 years. This suggests that the rate of carcinogenesis in individual cases has not been appreciably accelerated; instead more individuals have become susceptible and have developed the cancer at the prevailing rate.

TABLE II
Age at Death from Lung Cancer

Age Group (Years)	Expected Number of Deaths	Deaths Observed
40–49	0·48	2
50–59	2·30	5
60–69	5·70	14
70	1·66	3

Activity of Tuberculosis.—In the Queensland and Victorian cases, clinical evidence of activity of tuberculosis within the year preceding the first appearance of the lung cancer was found in 11 of the 24 cases. In the remaining cases the tuberculosis had been inactive for varying periods up to 30 years.

Incidence of Bronchitis or Other Chest Infection in Patients Developing Lung Cancer.—The records of the Victorian and Queensland cases revealed bronchitis to be a frequent coincidental finding in the patients developing lung cancer. In 14 of the 24 cases there was a history of bronchitis or recurrent pneumonia. In several cases, bronchitis preceded the diagnosis of tuberculosis, but more usually the condition followed the tuberculous disease.

THE SPATIAL ASSOCIATION OF TUBERCULOSIS AND LUNG CANCER

Method and Materials

In the Queensland and Victorian series previously described, there were 24 patients with tuberculosis who developed lung cancer. The records of these patients were available, but for geographical reasons the Western Australian patients could not be examined personally and have been excluded from this part of the investigation.

To determine whether the lung neoplasms developed more frequently than usual in the upper pulmonary lobes of persons with tuberculosis, the lobar site of each lung neoplasm was determined from the records and X-ray appearances. A case in which there were two primary neoplasms of different cell type was classified twice; consequently the lobar distribution of 25 lung neoplasms has been recorded.

The patients were also examined to determine the frequency with which the neoplasms developed in a region previously involved by tuberculosis. This presented certain difficulties, as the determination of the maximum extent of the tuberculosis depended upon the availability of previous X-ray films. In addition, suitable lateral films were seldom available to permit the determination of the segmental distribution of the disease. These difficulties were overcome by excluding patients who did not have a satisfactory series of X-ray films demonstrating the extent of the tuberculous disease before the malignant change developed, and by localizing the tuberculosis and cancer according to the radiological lung zones.

In five cases, the malignant disease was discernible in the earliest X-ray film available. In such circumstances, the presence of pre-existing tuberculosis at the site of origin of the malignant lesion is difficult to detect. Similarly, relevant earlier X-ray films were no longer available for five patients with pre-existing tuberculosis. In four of these five, radiologists' reports of the earlier X-ray films provided evidence that the subsequent lung cancer developed in an area previously involved by tuberculosis. However, as the reports could not be checked with the X-ray films, it was thought advisable to exclude these cases also.

For each of the 14 cases with adequate X-ray observation, all available X-ray films were inspected and the maximum involvement of tuberculosis was charted according to lung zones involved. The lung cancers were similarly classified according to lung zone. (The upper zones lie above the horizontal plane through the lower edge of the second intercostal cartilages; the middle zones lie between this plane and that through the lower edge of the fourth costal cartilages; the lower zones lie below this plane.)

Results

Thirteen of the 25 neoplasms originated in the right lung and 12 in the left. In contrast to the even distribution between the lungs, 17 (68%) of the 25 neoplasms arose in the upper lobe, whereas usually only 53% occur in the

upper lobes (Simons, 1937). The number of cases is small and the difference is not statistically significant; however, the frequency with which lung cancer develops in the upper lobes of persons with tuberculosis is consistent with a local intrapulmonary association of the two diseases. This becomes more apparent when an examination is made of the frequency with which lung cancer develops in the region of preexisting tuberculosis.

In the 14 cases in which X-ray observation was adequate, tuberculosis had involved a total of 38 lung zones, sparing the remaining 46. Lung cancer arose in 11 of the 38 tuberculosis-involved lung zones, and three times in the 46 uninvolved lung zones. This tendency for lung cancer to arise in an involved zone is significant ($0{\cdot}02 > P > 0{\cdot}01$).

VALIDITY OF RESULTS

In the epidemiological survey, patients were included in the tuberculous group provided they had been diagnosed as having tuberculosis and were ex-servicemen. With the exception of several patients who died rapidly from a malignant condition mistaken for tuberculosis, owing to the danger of introducing a bias, no attempt has been made to improve or correct the diagnosis of tuberculosis. This was determined by medical practitioners in three separate centres independently of this investigation and uninfluenced by it.

The tuberculous group included a small percentage of cases of extrapulmonary tuberculosis. In so far as the local effect of tuberculosis is related to the malignant process, the inclusion of non-pulmonary tuberculosis can be expected to have biased the series slightly against the possibility of finding an excess incidence of lung cancer.

That the tuberculous patients differed from the general population by being ex-servicemen provides a weakness in the statistical approach of a kind discussed by Berkson (1955). However, there is evidence that in England ex-servicemen have the same mortality from neoplasms as the general population. Case and Lea (1955) were able to show that British ex-servicemen with such a neutral condition as limb amputation have an identical incidence of malignant growths as the general male population. This is likely to be true for Australian conditions, especially as ex-servicemen form a large segment of the male population over the age of 30 years.

The possibility that persons with lung neoplasms may have been included in the tuberculous series because of the lung neoplasm requires exclusion. False diagnosis has been excluded; but the investigation of a person with lung neoplasm may lead to the discovery of tuberculosis which might otherwise have been undiscovered.

In 10 cases, tuberculosis and lung cancer were diagnosed within six months of each other. (In four cases, both tuberculosis and lung cancer were diagnosed simultaneously. In two cases the diagnosis of tuberculosis preceded that of lung cancer by three months. In four cases, tuberculosis was detected four to six months before the lung cancer.) Although lung cancer was probably present in all 10 cases when tuberculosis was first diagnosed, it is difficult to determine what proportion of the cases were brought to notice by the presence of the malignant lesion and not by tuberculosis. It is unlikely that all 10 cases entered the tuberculous series solely because of the presence of the malignant lesion. However, to allow for this remote possibility, all 10 cases can be provisionally excluded. The deaths from lung cancer are still significantly excessive (24 observed, 13 expected, $P=0{\cdot}03$).

Accuracy of Detection of Lung Cancer

The accuracy with which lung cancer is diagnosed will influence the frequency of its detection. The accuracy will depend upon clinical skill, the frequency of autopsy examinations and correction of incorrect certification. Of these factors, the skill of the medical attendants is unlikely to have varied considerably in determining the cause of death, with the exception that pulmonary tuberculosis frequently delayed the recognition of lung cancer. In two cases, lung cancer was not diagnosed for at least two years after its first appearance. In two other cases, inflammatory opacities completely obscured a fatal pulmonary neoplasm. In an unknown number of cases, the presence of tuberculosis may have entirely masked a lung neoplasm.

On the other hand, the percentage of post-mortem examinations performed on subjects from the tuberculous group was probably higher than amongst the general population. This would have a tendency to exaggerate the excessive incidence of lung cancer in the tuberculous group. However, from the information available concerning the incidence of post-mortem examinations in the general population and in the tuberculous group, the difference is quite insufficient to have caused more than a very minor variation between the incidences of carcinoma in the two groups.

On the other hand, cases in which the subject was recorded as having died from malignant

disease in the tuberculous group, but not those in the general population, were examined for clerical and clinical errors. This had the effect of minimizing the excess incidence of lung cancer amongst the tuberculous group in the following manner. Of those originally recorded as having died from carcinoma of the lung in Queensland and Victoria, four were excluded from this investigation. In two cases the original diagnosis of cause of death was not supported by post-mortem examination, and in a third case carcinoma of the lung had been mistakenly diagnosed as tuberculosis. The fourth case was excluded because the diagnosis of tuberculosis had been made in retrospect on scant grounds, after death had occurred from carcinoma of the lung. A case recorded as one of carcinomatosis was added to the deaths from lung cancer from autopsy evidence.

Errors in the opposite direction—that is, deaths incorrectly recorded as being due to non-malignant conditions—have not been corrected, owing to the magnitude of the task and to the fact that community deaths are not corrected. For this reason, one patient known to have died from carcinoma of the lung, but recorded incorrectly as having died from pulmonary tuberculosis, has not been included in the series as having died from lung cancer. This one-sided correction of errors is likely to have produced a slight bias, whereby deaths from carcinoma of the lung have been minimized. The finding of an excess mortality from lung cancer in these circumstances is of added significance.

Various Associations which may have Increased the Incidence of Lung Cancer

An epidemiological study differs from an animal experiment by the fact that the experimental group is selected by the possession of the characteristics to be investigated. This has a definite disadvantage, as it remains uncertain whether or not the individuals with the chosen characteristics will vary from the population in other ways. For this reason, the epidemiological investigation cannot prove a causal relationship with the apparent finality of the animal experiment. The problem can be partly overcome by examining the groups for other likely influences and eliminating these as significant factors. In the present investigation various possible relationships require examination.

Tobacco Smoking Habits

The smoking habits of the patients who developed lung cancer were not recorded in all instances. In Queensland and Victoria, 19 had been questioned concerning their smoking habits. All were smokers, although two had abandoned the habit before the carcinoma developed.

The question to be decided is whether or not cigarette smoking alone can explain the excessive incidence of lung cancer amongst tuberculous patients. As will be shown, there is evidence against this contention, as the difference between the smoking habits of the tuberculous patients and those of the male population, corrected for age, would need to be of an unexpectedly extreme degree to produce the observed excess of pulmonary neoplasm.

The effect of the smoking habits of tuberculous patients can be illustrated by the data of Lowe (1956), who found that patients with tuberculosis prior to diagnosis smoked more than controls. Edwards (1957) calculated that, in comparison with non-smokers, the incidence of pulmonary cancer would be increased sevenfold by the smoking habits of Lowe's controls. If the same method of calculation is used, the smoking habits of Lowe's tuberculous patients would increase the incidence of pulmonary cancer eightfold in comparison with non-smokers.

Therefore, compared with the non-tuberculous population, the smoking of tuberculous patients will increase the expected incidence of pulmonary malignant disease by only eight-sevenths. This is insufficient to account for the observed increase in the present series. Moreover, this is almost certainly an over-estimation, as it is based upon the smoking habits before diagnosis of tuberculosis, whereas tuberculous patients decrease their smoking after diagnosis. Of 306 tuberculous patients questioned in Queensland, 9·1% were non-smokers when tuberculosis was diagnosed, whereas 24·8% were non-smokers after treatment. Of 221 controls, 19·9% were non-smokers.

On present evidence, it is impossible to explain the excess mortality from lung cancer solely by the smoking habits of the tuberculous patients.

The Effect of Occupation and Social Class

The incidence of lung cancer is known to be higher in certain occupations, and is slightly influenced by social class (Logan, 1959). However, exposure in trades with an occupational risk from lung cancer was not a feature of a random sample of 302 tuberculous patients attending the Repatriation Out-Patient Chest Department in Brisbane. Similarly, although there was an excess of persons in the lower-paid

manual occupations, this divergence from the male population was insufficient to account for the excessive incidence of lung cancer'

The Effect of Radiation

In the course of management of their disease, patients with tuberculosis may be exposed to greater X-radiation than the general population. However, this radiation is most unlikely to be sufficient to influence the incidence of lung cancer. The amount of radiation from chest X-rays films is not great, and it has been found that the incidence of lung cancer amongst British radiologists is not excessive (Court-Brown and Doll, 1958).

The Effect of Chemotherapy

Anti-tuberculosis chemotherapy has been in vogue for the last 10 years. There has been no evidence to suggest that streptomycin, PAS or isoniazid is carcinogenic. Moreover, chemotherapy had been administered to only six of the 24 patients who developed lung cancer in the Victorian and Queensland series.

DISCUSSION

As there is no convincing evidence of a major hereditary factor in the development of lung cancer, and because of the importance of environmental determinants of tuberculosis, a diathesis linking tuberculosis and cancer would be a remote possibility. Moreover, the spatial association of the two diseases favours the existence of a local influence rather than a diathesis which is less likely to cause the lung cancer to arise at the site of the tuberculosis.

In the absence of other likely explanations, it is possible to advance the hypothesis that tuberculosis has in some way contributed to the excess incidence of lung cancer.

Provided that there is no independent tendency for lung cancer to develop more frequently in the upper lobes, the frequent occurrence of lung cancer in parts of the lungs previously involved by tuberculosis adds to the likelihood of a causal relationship. It is of interest that the tuberculous process had often become of minor extent and was often inactive by the time the malignant disease developed. This suggests that any causal effect may be of a non-specific nature, rather than due to the specific influence of the tubercle bacillus.

Lung scarring and chronic bronchitis are frequently caused by pulmonary tuberculosis. There is evidence that both lung scarring (Raeburn and Spencer, 1953; Gelzer, 1956; Burgel and Themel, 1958) and chronic bronchitis (Case and Lea, 1955; Denoix *et alii*, 1958) are probably related to the development of lung cancer.

These findings can be linked with other accounts of the development of lung cancer in inflammatory lesions. Spain (1957) described the frequency of chronic inflammation and interstitial fibrosis apparently preceding terminal bronchiolar carcinoma. In two of the 12 cases, the inflammation was due to old tuberculous lesions. Feofilov (1958) found nine out of 20 patients with lung cancer with previous inflammatory changes which could be regarded as the trigger factor for lung cancer. Richards and Milne (1958) and Caplan (1959) discuss the apparent predisposition to lung cancer brought about by the pulmonary lesions of scleroderma.

Several hypotheses have been advanced to explain the development of lung cancer in scars. Raeburn and Spencer (1953) have described epithelial hyperplasia and metaplasia at the site of some lung scars, and they postulate that these changes may proceed to produce malignant disease.

In addition, Kennaway (1957) quotes Raeburn as having demonstrated that the lung scars in which lung cancer develops are rich in cholesterol:

> This proximity of cholesterol to malignant growth is of great interest in view of the discovery by Heiger (1949) of the carcinogenic power of cholesterol, which is not diminished by drastic purification (Schwenk process). Of course the juxtaposition of these crystals and a carcinogen is very far from proving that one is the cause of the other, but what more evidence can one expect from histological appearances.

Blacklock (1957) has suggested a mechanism by which cholesterol in lung scars may predispose the lung to carcinogens. He states that it "may well be that cholesterol deposits act as a solvent for any carcinogen that gains access to the tissues and thus the carcinogen is concentrated at that site". Experimentally he demonstrated that pellets of cholesterol containing dissolved benzpyrine or methylcholantherine would cause cancer of the lung of rats.

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Australia, provided the list of actual deaths amongst the tuberculosis patients in Western Australia. Dr. N. Tennant made available the occupations of tuberculous patients and assisted in the investigation of their smoking habits. The information relating to the smoking habits of the controls was gathered with the assistance of Professor Douglas Gordon by Miss M. Daly, Miss E. Larsen and Mr. T. G. Lithgow. Mr. L. Ladlay, Mr. N. De Hugard and Miss G. Thomas, of the Repatriation Department, have all assisted in compiling the material. Thanks are due to all who have assisted, and to the Chairman of the Repatriation Commission for permission to use the clinical material and publish this report.

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THE INCIDENCE OF TOXOPLASMA ANTIBODIES IN MENTAL HOSPITAL PATIENTS[1]

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SUMMARY

Of 342 inmates of a mental hospital, 19 possessed complement-fixing and 60 dye-test antibodies against *Toxoplasma gondii*.

The incidence of complement-fixing antibodies was less in the hospital patients than in the general population. This suggests that the risk of post-natal infection with *Toxoplasma* was less in the hospital environment than outside.

Among 116 children with congenital mental deficiency of unspecified ætiology, there was serological evidence that *Toxoplasma* was a possible cause in eight, or 7%, but in none was this confirmed by the presence of chorio-retinitis or cerebral calcification.

In the patients studied, toxoplasmosis was at most only a rare cause of congenital mental deficiency.

ANTIBODIES against *Toxoplasma gondii* are widespread in the general population of Queensland. In a series of 760 cases, Cook (1959) found complement-fixing (C.F.) antibodies in 13% and dye test (D.T.) antibodies in 24%. The infection producing these antibodies is nearly always symptomless, but occasional cases of overt infection have been recognized—congenital or acquired—with ocular, glandular or myocardial involvement (Cook, 1959; O'Reilly, 1954). The widespread activity of the parasite in Queensland and its known tendency in congenital cases to attack and damage the brain prompted a survey of juvenile mental hospital patients to determine to what extent it might be a cause of mental deficiency.

The Ipswich Mental Hospital was chosen for this survey, as it accepts nearly all children in Queensland who require admission for mental disorder. As a rule, they are not transferred away on growing up. This hospital also holds two other categories of patients: (i) a group arrested for offences ranging from disorderly conduct to murder and then found to be psychotic; (ii) chronic psychotics, remaining from a period when the current policy was to transfer this type here.

The sera of 342 patients—that is, practically all those under the age of 50 years—were tested for C.F. and D.T. antibodies by the methods described by Cook and Pope (1959) and by Cook (1959). The results are shown in detail in Table I. Nineteen sera reacted to the complement-fixation test at a titre of 1 : 4 or more, and 60 to the dye test at 1 : 16 or more. Twenty-six of the sera gave a non-specific reaction in the complement-fixation test with the normal antigen and six were anticomplementary. Many of these patients were retested, but the second sample of serum was again unsuitable.

INCIDENCE OF ANTIBODIES IN RELATION TO AGE AND SEX

The general population shows a rapid increase in both C.F. and D.T. antibodies around the age of 15 years, indicating that in Queensland the greatest liability to invasion with *Toxoplasma* exists at this age. In the hospital patients, the incidence of C.F. antibodies was much less than in the general population (Figure I). This suggests that hospital life had offered some protection from infection, and it is in accord with this suggestion that the difference was particularly noticeable at 15 to 29 years of age—that is, immediately after the age when the risk of infection outside the hospital is greatest. (However, in no age group did the difference exceed twice its standard error, although it almost reached significance at 15 to 19 years—1·9 times the standard error.)

The incidence of D.T. antibodies was less in the hospital patients aged under 20 years than in the general population, but greater in the older age groups. None of these differences was significant.

To assess the significance of the antibody incidence in any section of the hospital patients, it is necessary to take into account the age structure. For each section an "expected

[1] Received on January 3, 1961.

[2] Research Officer, Queensland Institute of Medical Research.

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number" may be calculated. This is the number of patients who would possess antibodies if the incidence in each age group was the same as in the general population.

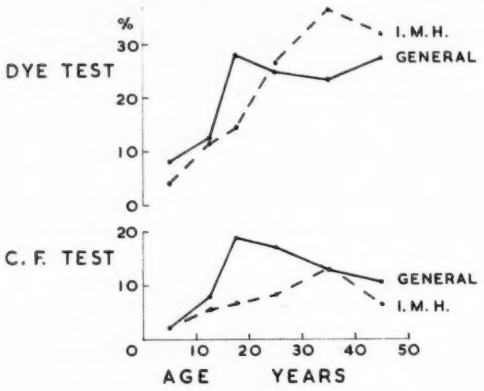

FIGURE I

Comparative incidence of *Toxoplasma* antibodies in Ipswich Mental Hospital patients, compared with that in the general population as found by Cook (1959). Complement-fixing antibodies were less frequent in the hospital than outside it, particularly in those aged between 15 and 30 years. Dye test antibodies were, on the whole, equally frequent in the two situations

For all the patients (Table II), the number expected to have C.F. antibodies was 32, as against the actual number of 19. The difference is not quite significant ($\chi^2=3\cdot1$, $P<0\cdot1$). The number with D.T. antibodies was close to the expected number.

When male and female patients were analysed separately, it was seen that the low incidence of C.F. antibodies was equally evident in each sex.

ANTIBODIES IN RELATION TO PERIOD SPENT IN HOSPITAL

The Ipswich Mental Hospital occupies 146 acres on the outskirts of Ipswich. It houses about 600 patients, who are cared for by a resident staff of about 50 (with dependants) and a non-resident staff of about 300. Many male patients are employed on the farm. The stock includes 60 cows, seven horses and two dogs, but no poultry. The cows are pastured on grass; from time to time maize, sorghum, oats and cowpeas are grown for them. A range of vegetables is produced for hospital use, and there are orange, loquat and mango trees. Females and children would have little or no association with the farm animals, but would make contact with pet cats and an occasional dog. Pigeons are numerous in the hospital grounds; tissues from 58 were inoculated into mice in 11 pools, but *Toxoplasma* was not isolated. Horses are stabled in a neighbouring property throughout most of the year.

In Table II, the results of the survey have been analysed according to the period in hospital. This period was not always clear-cut. Some patients had been discharged and readmitted. With these, and with those transferred from

TABLE I

Serological Survey of Mental Hospital Patients for Toxoplasma Antibodies

Age Group (Years)	Sex	Totals	Complement-Fixation Test Results									Dye Test Results										
			Non-Specific or Anti-complementary	Negative	Number Positive at Reciprocal Titre: 4	8	16	32	64	128	Positive[1] (*per Centum*)	Negative	Number Positive at Reciprocal Titre: 16	32	64	128	256	512	1024	2048	4096	Positive (*per Centum*)
0– 4	M.	12	2	10	—	—	—	—	—	—	—	12	—	—	—	—	—	—	—	—	—	—
	F.	10	2	8	—	—	—	—	—	—		10	—	—	—	—	—	—	—	—	—	
5– 9	M.	31	5	26	—	—	—	—	—	—	3	30	—	—	1	—	—	—	—	—	—	5
	F.	45	2	41	—	1	1	—	—	—		42	1	—	—	—	1	1	—	—	—	
10–14	M.	23	3	20	—	—	—	—	—	—	6	21	1	—	—	—	—	—	1	—	—	12
	F.	37	3	31	1	—	1	—	—	1		32	2	1	—	—	1	—	—	—	1	
15–19	M.	28	4	22	1	1	—	—	—	—	7	22	2	1	2	—	1	—	—	—	—	14
	F.	21	—	20	1	—	—	—	—	—		20	—	—	1	—	—	—	—	—	—	
20–29	M.	27	3	21	1	1	1	—	—	—	8	19	3	1	1	—	2	1	—	—	—	27
	F.	25	1	23	—	1	—	—	—	—		19	4	1	1	—	—	—	—	—	—	
30–39	M.	23	2	19	1	1	—	—	—	—	13	15	5	—	1	2	—	—	—	—	—	36
	F.	10	1	7	—	2	—	—	—	—		6	—	—	1	2	—	1	—	—	—	
40–49	M.	32	2	27	1	2	—	—	—	—	7	20	6	1	3	1	1	—	—	—	—	32
	F.	18	2	16	—	—	—	—	—	—		14	2	1	—	—	1	—	—	—	—	
Total	M.	176	21	145	4	5	1	—	—	—	6	139	17	3	8	3	4	1	1	—	—	18
	F.	166	11	146	2	4	2	—	—	1		143	9	3	3	2	3	2	—	—	1	

[1] In calculating this percentage, non-specific or anticomplementary results were excluded from the denominator.

another mental hospital or from prison, the "period in hospital" was calculated from the first admission. Some patients were frequently allowed out on leave, and many were regularly taken on excursions and picnics.

The incidence of C.F. antibodies was slightly less than expected in those with under ten years' stay, and much less in those with over ten years' stay. While the differences between actual and expected incidence are not statistically significant, the increasing disparity with longer stay supports the suggestion made above that exposure of patients to *Toxoplasma* is less in the hospital environment than outside. The low incidence also argues against the spread of *Toxoplasma* from case to case, as the opportunities for case-to-case infection, both by respiratory and alimentary routes, are frequent in mental institutions.

TABLE II

Incidence of Antibodies, Actual and Expected, in Relation to Sex and Period in Hospital

TABLE IIA

Sex	Number of Cases	Complement-Fixation Test: Cases with Titre of 1 : 4 or Over	Complement-Fixation Test: Expected Number	Dye Test: Cases with Titre of 1 : 16 or Over	Dye Test: Expected Number
Males ..	176	10	17	37	35
Females ..	166	9	15	23	28·5
Total ..	342	19	32	60	63·5

TABLE IIB

Period in Hospital (Years)	Number of Cases	Complement-Fixation Test: Cases with Titre of 1 : 4 or Over	Complement-Fixation Test: Expected Number	Dye Test: Cases with Titre of 1 : 16 or Over	Dye Test: Expected Number
0 to 4 ..	132	6	7·5	14	17
5 to 9 ..	84	5	8	16	14·5
10 and over	126	8	16·5	30	32
Total ..	342	19	32	60	63·5

The incidence of D.T. antibodies was close to that expected in each group. The difference in this respect from the C.F. results may perhaps be related to the longer persistence of D.T. antibodies. Although there is much individual variation, the presence of C.F. antibodies usually implies infection within the last few years, whereas D.T. antibodies, particularly if in low titre, may be the consequence of infection many years earlier. In Case 12, the height of the D.T. titre—1 : 4096—indicated fairly recent infection, and this probably applies also to the titre of 1 : 1024 in Case 314. Each child had been in hospital only four years, so that the infection could have begun before admission.

ANTIBODIES IN RELATION TO TYPE OF MENTAL DISORDER

In Table III, the results of the tests have been analysed according to the mental disorder, and expected numbers calculated for each category.

TABLE III

Incidence of Antibodies, Actual and Expected, in Relation to Type of Mental Disorder

Mental Classification	Number of Cases	Complement-Fixation Test: Number with Titre of 1 : 4 or Over	Complement-Fixation Test: Expected Number	Dye Test: Number with Titre of 1 : 16 or Over	Dye Test: Expected Number
Congenital mental deficiency:					
Mongolism	32	1	2	1	4
Special syndromes	8	0	1	0	2
Hydrocephalus	6				
Microcephaly	42	1	2·5	2	5
Not elsewhere included	178	10	18·5	31	34
Post-encephalitic disorder, etc.	15	1	1	2	2
Schizophrenia	53	6	6	19	14
Miscellaneous	8	0	1	5	2
Epilepsy[1] ..	89	5	8	17	15

[1] The epileptics are all included in other classifications in the first part of the table.

Congenital Mental Deficiency

These cases formed a heterogeneous group and included some distinctive syndromes. In many, a clear history of the onset was not available and they were classified as congenital on probability.

The one mongoloid patient with antibodies (C.F. 1 : 4, D.T. 1 : 256) was a male, aged 23 years, who had been in hospital for 18 years and worked in the garden. As mongolism has a genetic ætiology, his toxoplasmic infection would be incidental.

The "special syndromes" consisted of two cases of Sturge-Weber syndrome, one each of Schilder's disease, oxycephaly, tuberous sclerosis, porencephaly, congenital syphilis and phenylketonuria. The patient with tuberous sclerosis showed intracranial calcification.

Hydrocephalus and microcephaly are common in congenital toxoplasmosis, but in this series the incidence of antibodies was less than expected in each group. A patient was classified as microcephalic when the head circumference was at least three standard deviations less than the

TABLE IV

Details of 12 Patients with Congenital Mental Deficiency and Toxoplasma Antibodies

Case Number	Birthplace	Sex	Age (Years)	Age on Admission (Years)	Complement-Fixation Titre (Reciprocal)	Dye Test Titre (Reciprocal)	Chorio-retinitis	Cerebral Calcification	Circum-ference of Head (Inches)	Epilepsy or Convulsions
84	Sydney, N.S.W.	F.	7	7	16	512	—	—	18¾[1]	+
305	Not recorded	M.	8	5	N.S.[2]	64	—	—	20½	—
72	Brisbane	F.	9	4	8	256	—	—	19½	—
94	Bundaberg, Qld.	F.	9	8	N.S.[2]	16	—	—	19½	+
75	Not recorded	F.	10	6	—	16	—	—	21	+
80	Brisbane	F.	11	5	16	256	—	—	20	—
314	Brisbane	M.	12	8	N.S.[2]	1024	—	—	21	+
321	Cairns, Qld.	M.	13	4	N.S.[2]	16	—	—	18½[1]	—
179	Not recorded	F.	13	6	N.S.[2]	16	—	—	22	+
12	Germany	F.	14	10	128	4096	—	—	20½	+
194	Not recorded	M.	19	1·5	—	256	+	—	20½	—
14	Blair Athol, Qld.	F.	25	12	—	16	+	—	20	+

[1] Classified as microcephalic.
[2] Non-specific.

mean found by Westropp and Barber (1956) for the appropriate age and sex. Westropp and Barber's series ended at seven years; for those older than this, the circumference as at seven years was adopted as standard. Microcephalic mongoloid subjects were included in the mongolism group. Details of the two microcephalics with antibodies are given in Table IV.

Post-Encephalitic Mental Disorder, etc.

Fifteen patients, three male and 12 female, had a history of an acute illness from which the mental symptoms dated, at ages from nine weeks to seven years. The most frequent diagnoses were encephalitis and meningitis. A girl, aged 14 years, with a history of encephalitis at the age of three years, had antibodies at low titres to each test (C.F. 1 : 4, D.T. 1 : 32), and a girl, now aged 18 years, who had measles encephalitis at seven years, had D.T. antibodies to a titre of 1 : 16.

Schizophrenia

The schizophrenics were much older than the groups already discussed; most were aged over 30 years. Males comprised 45, females eight. The excess of D.T. antibodies is not significant ($\chi^2=0{\cdot}70$, $P>0{\cdot}3$). In no case was the C.F. titre more than 1 : 8. The D.T. titres were 1 : 16 (9), 1 : 64 (5), 1 : 128 (3), 1 : 256 (2).

Miscellaneous Conditions

This group comprised manic-depressive psychosis (4), epileptic psychosis (2), moral deficiency and paraphrenia.

Epilepsy

Our results are in accord with those of Feldman (1958), who has found congenital toxoplasmosis not to be unduly frequent in epileptic children.

CONGENITAL TOXOPLASMOSIS AS A CAUSE OF MENTAL DEFICIENCY

To what extent is congenital toxoplasmosis a cause of mental deficiency?

In an attempt to answer this question, the most important cases to consider are those in which the patients are aged under 15 years. D.T. antibodies resulting from congenital infection may be expected usually to persist through this period. The presence of antibodies does not imply that symptoms are necessarily due to toxoplasmosis, but their low incidence in the general population in this age group gives them more diagnostic significance than at later ages. The younger the patient, the more likely are the antibodies to be due to congenital infection.

In the present series, the cases of mongolism and of the special syndromes mentioned may be excluded from the total, as suspicion of a toxoplasmic ætiology does not arise with them. There remain 116 patients with congenital mental deficiency aged under 15 years, in 10 of whom D.T. antibodies were present (Table IV). In two of these the titre seems too high for the antibodies to have dated from birth; Case 12, C.F. and D.T. titres of 1 : 128 and 1 : 4096 respectively at the age of 14 years; Case 314, D.T. titre of 1 : 1024 (and a non-specific C.F. result) at 12 years. In the other eight cases the titres seem compatible with congenital infection, although the considerable individual variation in antibody response makes a definite decision on the point impossible. This suggests 8/116 or 7% as an upper limit for the proportion of cases in this group that might have been caused by congenital toxoplasmosis. In subjects aged under five years, the proportion was 0/17; in those aged five to nine years, 4/51; in those aged 10 to 14 years, 4/48.

Confirmation of the diagnosis may be sought from clinical studies. In 180 American cases of congenital toxoplasmosis, Feldman (1958) noted the following main clinical manifestations: chorio-retinitis, 94%; cerebral calcification, 59%; psychomotor retardation, 45%; convulsions, 39%; microphthalmia, 36%; hydrocephalus, 22%; microcephaly, 21%. It follows from these figures that the presence of chorio-retinitis would be almost essential for a diagnosis of congenital toxoplasmosis, and strong support would be given by cerebral calcification. Neither feature was present in any of the 10 Ipswich children with antibodies. However, Thalhammer (1960) in Vienna has concluded on statistical grounds that mental deficiency, particularly of milder grades, can be due to prenatal toxoplasmic encephalitis without chorio-retinitis or calcification.

We may conclude that the proportion of congenital mental deficiency in these patients caused by congenital toxoplasmosis lies between 0 and 7%, probably nearer to the lower figure.

It was earlier noted (Table III) that the number of congenital mental defectives with D.T. antibodies was close to that expected in the general population. This was true also for the 0 to 14 years age group (10 found, 11·6 expected), and this confirms the conclusion that the amount of congenital mental deficiency due to toxoplasmosis is quite small.

The incidence of antibodies at Ipswich is not unlike what Burkinshaw *et alii* (1953) found in a survey of certified mental defectives in London. Of 503 under the age of 15 years, 22, or 4·4%, reacted to the toxoplasmin skin test. In no case could the mental defect be definitely attributed to toxoplasmosis. However, Thalhammer considered that 17% of 364 cases of congenital damage to the brain in Vienna were caused by toxoplasmosis. His higher figure may be explained in part by his concept mentioned above of toxoplasmic encephalitis without chorio-retinitis or calcification, and by his acceptance of a D.T. titre of 1 : 4 as indicating infection.

There were 42 Ipswich patients with congenital mental deficiency (excluding mongolism and special syndromes), aged from 15 to 19 years, of whom five, or 12%, had antibodies; and 41, aged from 20 to 29 years, of whom 11, or 27%, had antibodies. At these ages there is a rapidly decreasing likelihood that antibodies are due to congenital infection. Two of the 16 patients had chorio-retinitis, none had cerebral calcification.

Case 194 was that of a male spastic diplegic idiot aged 19 years, admitted to the hospital at the age of 18 months. Examination of his eyes showed nystagmus, a large area of chorio-retinitis in the right eye including the macula, and left optic atrophy.

Case 14 was that of a female idiot, aged 25 years who "since birth has been utterly incapable of doing anything". She has a left macular chorio-retinitis.

These two patients probably had congenital toxoplasmosis. The absence of C.F. antibodies (Table IV) is in accord with an infection that began many years before.

ACKNOWLEDGEMENTS

Our thanks are due to Dr. A. Fryberg, Director-General of Health and Medical Services, and Dr. B. F. R. Stafford, Director of Mental Hygiene, for facilitating this survey, to Dr. R. A. Atherton, Medical Superintendent of the Ipswich Mental Hospital, and his staff for their cordial cooperation, to Dr. H. P. Spiro and Dr. M. R. Harrison for the examination of eyes, to Dr. A. H. B. Clarke and Dr. R. Row for the radiography, to Dr. R. L. Doherty, Mr. W. Scott and Sister E. M. Roveta for assistance with taking blood from patients, and to Dr. H. R. G. Barrett, Dr. W. Leggat, Dr. B. Geaney, Dr. B. S. Purssey, Dr. W. D. Richards and Dr. N. R. Scott-Young for assistance in various ways. It was a privilege to discuss the results with Dr. Leon Jacobs, of Bethesda, U.S.A., during his visit to Brisbane.

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CHANGES IN THE ELECTROCARDIOGRAM AFTER OPEN HEART SURGERY[1]

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SUMMARY

This is a study of the electrocardiograms of 23 patients who had undergone open heart surgery—repair of an atrial septal defect in 10, and in 13 closure of a ventricular septal defect, some with and some without an associated pulmonary infundibulectomy.

A variety of supraventricular arrhythmias were noted after the repair of an atrial septal defect. Possible ætiological factors include atrial irritability, pericarditis and electrolyte changes. Arrhythmias noted after the closure of a ventricular septal defect consisted of ventricular fibrillation during or immediately after the operation. This could be more clearly attributed to the direct trauma of surgery or to electrolyte shifts at the time of surgery.

There were decreases in the height of the *P* waves and a diminution of the *P-R* interval after the repair of atrial septal defects. These changes appear to be related to improved atrial conduction and the decreased size of the right atrial chamber. Elimination of the left-to-right shunt after operation probably explains these findings.

The proximity of a defect of the ventricular septum to the known anatomical pathway of conduction along the right bundle correlates with the right bundle branch block or delay in the activation of the right ventricle which is noted after the repair of these defects.

This study confirms the association of pulmonary infundibulectomy with the appearance of a type of right bundle branch block. However, this association did not occur when a lateral excision of tissue from the pulmonary outflow tract was performed. This emphasizes the importance of damage to the superiorly located crista supraventricularis in the genesis of right bundle branch block after infundibulectomy.

The occurrence of the major *QRS* vector change after the completion of the first 0·04 second of the complex suggests that the later portions of the *QRS* complex are inscribed after a surgically imposed block has been encountered.

The presence of *S-T* segment elevation after surgery for both atrial and ventricular septal defect repair probably correlates with the pericardial reaction and inflammation which one might expect. We learn that the electrocardiographic evidence of such change may last from four to at least 14 days after surgery.

The changes noted in the mean *T* wave vector suggest that the repolarization of the ventricles is altered in a fairly consistent fashion after the repair of an atrial septal defect, and in a varied manner after the repair of a ventricular septal defect. The *T* wave changes in precordial leads after surgery are probably due to a number of factors, including anoxia and injury.

THE rapidly expanding field of open heart surgery has permitted the manipulation and alteration of existing cardiac structure to an extent which had previously been impossible. These structural changes accompanied by the trauma of surgery itself can produce changes in the electrocardiograms of the patients who undergo such operations.

One may expect the electrocardiogram to reflect two types of change. The trauma of the operation may produce immediate effects. An alteration in the size and shape of the cardiac chambers because of a change in hæmodynamics may produce additional changes.

There have been some reports describing alterations in the electrocardiogram which have resulted from the trauma of open heart surgery. Lillehei noted the occurrence of right bundle branch block following the repair of

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some defects of the membranous portion of the ventricular septum (Kirklin *et alii*, 1953). Zimmerman and co-workers (1958) described the appearance of a pattern similar to right bundle branch block following the resection of the crista supraventricularis. In addition, Sasaki and his colleagues (1958) have analysed arrhythmias attending the repair of atrial and ventricular septal defects. The purpose of this paper is to report additional changes in the electrocardiogram.

MATERIALS AND METHODS

The pre-operative and post-operative electrocardiograms of 23 patients who had undergone cardiac bypass surgery were studied. The pre-operative electrocardiograms were standard twelve-lead records and were all taken within six months prior to surgery. The post-operative tracings were recorded during the first two weeks. At least three electrocardiograms from each patient were included. Because of the presence of chest bandages, only the limb leads were obtained in the electrocardiograms of the first week, but at least one record obtained during the second week included all 12 standard leads.

The patients were selected at random from each of the following two groups, according to the operative procedure:

(1) Atriotomy with repair of an ostium secundum atrial septal defect: 10 patients were studied. They did not have significant pulmonary hypertension prior to surgery. These patients varied in age from 5 to 43 years, with an average of 13 years. Half the patients were aged 10 years or under.

2. Ventriculotomy with repair of a ventricular septal defect: 13 patients were studied. Seven of these had a pulmonary artery systolic pressure greater than 30 mm. Three patients underwent a pulmonary infundibulectomy in addition to a septal repair. The age ranged from 5 to 20 years, the average being 12 years. Half the patients were aged 10 years or under.

The following measurements were made: (i) the heart rate and rhythm; (ii) the *P-R* interval; (iii) the *QRS* complex duration; (iv) the *Q-T* interval; (v) the axis in the frontal plane for the *P*, *QRS* and *T* waves; (vi) the height of the *P* wave in lead V_2; (vii) the height of the *R* wave and the depth of the *S* wave in leads V_1, V_2 and V_5. A direct-writing electrocardiographic machine was used (Sanborn Company, Model No. 51).

FINDINGS

Arrhythmias

All patients had normal sinus rhythm before surgery with two exceptions. One patient with an atrial septal defect had sinus tachycardia and another patient with the same defect had second-degree heart block.

Sinus tachycardia was common after surgery, occurring in seven of the 10 cases studied after the repair of an atrial septal defect, and in all the 13 patients who underwent the repair of a ventricular septal defect.

Atrial Septal Defect.—One patient acquired a nodal pacemaker which persisted through the second week after operation. Another developed a nodal rhythm with atrio-ventricular dissociation, which progressed to atrial fibrillation and finally to sinus rhythm. A third developed supraventricular tachycardia which changed to a wandering pacemaker.

Ventricular Septal Defect.—Arrhythmias of long duration did not occur, and even premature ventricular beats were rare. Three patients from this group developed ventricular fibrillation, which occurred during the closure of the heart or upon restarting of the heart beat after elective cardiac arrest; but these patients reverted to sinus rhythm after electric defibrillation.

P Waves and P-R Interval

Atrial Septal Defect.—There were definite changes in the *P* wave and *P-R* interval after operation. Before operation, five patients had abnormal *P* waves. Four of these had tall peaked *P* waves (from 2 to 4 mm. in height) in lead V_2. These were outside the maximal range according to age in a study of 500 normal tracings (Lepeschkin, 1951). One patient had broad notched *P* waves (in leads I and II). A decrease in the height of the *P* wave in lead V_2 occurred in all cases by the end of the second week after operation (Figures I and III). The average decrease was 1·2 mm. There was also a decrease in the height of the *P* waves in specific limb leads. The average height of the tallest *P* wave in the frontal plane decreased from 1·4 to 0·8 mm. during this period. However, there were concomitant shifts in both directions of the frontal plane axis. Six patients showed a leftward shift (10° to 180°) and three patients showed a rightward shift (10° to 60°). One patient showed no significant change. The *P-R* interval was abnormally prolonged prior to surgery in two patients with an atrial septal defect. The *P-R* interval became shortened in all 10 patients in the immediate post-operative period. This change persisted in eight of the

10 patients even after the heart rate had slowed to normal values (Figure II).

Ventricular Septal Defect.—Three patients had abnormal *P* waves prior to surgery. One patient had tall *P* waves (2·5 mm. in lead V_2) and two patients had notched *P* waves (seen in the limb leads in one case and in all leads

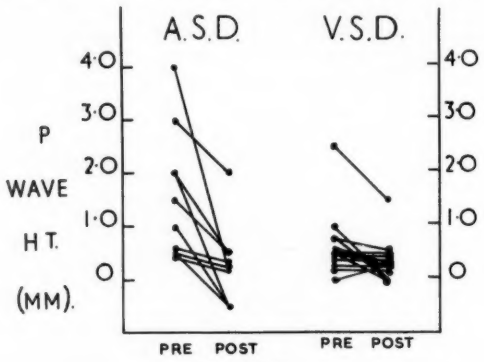

FIGURE I
Operative change in height of *P* waves in lead V_2

in the other case). Most of the patients showed no change in the height of the *P* wave in lead V_2 after the repair of a ventricular septal defect (Figure I). Only four patients showed a decrease in the height of the *P* wave of greater than 0·5 mm. Likewise, most of these patients showed no significant change in the *P* wave axis

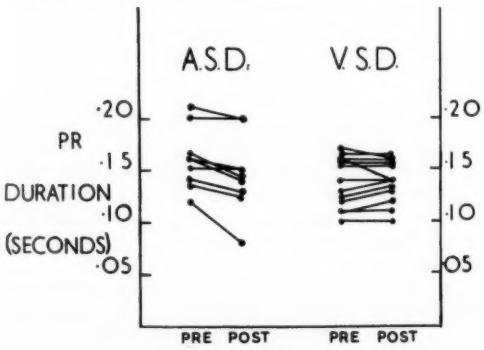

FIGURE II
Operative change in *P-R* interval

in the frontal plane. The four patients showing a change had shifts of axis in each direction (average 40°). The *P-R* interval was not prolonged before operation in any of these patients, and it was not significantly shortened after surgery (Figure II).

The duration of the *P* waves was not significantly altered by either type of operation.

QRS Complex

Atrial Septal Defect.—An *rSR'* pattern in leads V_1 and V_2 was noted before operation in eight patients. Half of these had a *QRS* complex duration prolonged to 0·10 or 0·11 second, and an incomplete right bundle branch block was diagnosed. Seven patients had electrocardiographic evidence of right ventricular hypertrophy. After surgery, four patients had a persistent diminution in the duration of the *QRS* complex after tachycardia had ceased. An incomplete right bundle branch block could no longer be diagnosed in three of these cases.

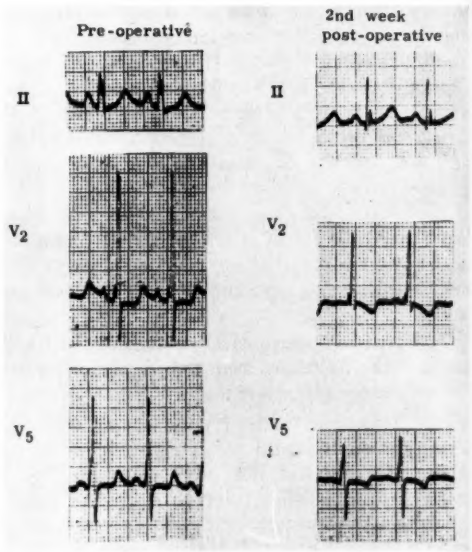

FIGURE III
Pre-operative and post-operative tracings of a patient who had an atrial *secundum* defect. Note the decrease in the height of the *P* waves and the *T* wave changes

There had been a decrease in the height of the *R* or *R'* waves in leads V_1 and/or V_2 in six cases. These changes were not sufficient, by the second week, to alter the previous diagnosis of right ventricular hypertrophy. We did not observe a consistent shift in the *QRS* axis in the frontal plane among these patients with atrial septal defect repair.

Ventricular Septal Defect. — Electrocardiographic diagnosis of right ventricular hypertrophy was suggested or definitely present in the tracings of five patients prior to surgery. Left ventricular hypertrophy was not diagnosed in any. After operation, the greatest change noted was a decrease in the voltage of the sum

TABLE I

Showing Presence of Pre-Operative Pulmonary Hypertension, Surgical Problem and Post-Operative Electrocardiographic Changes in Patients who had Repair of a Ventricular Septal Defect

Patient	Type of Defect	Infundibulectomy	Pulmonary Hypertension	Post-Operative Electrocardiogram
1. R.H.	8 mm. long; tubular	Yes	—	Complete right bundle branch block
2. W.P.	2 mm. in diameter; above insertion of tricuspid valve	—	Yes	Complete right bundle branch block
3. P.V.	8 mm. in diameter; in membranous septum	—	Yes	Complete right bundle branch block
4. P.J.	14 mm. in diameter; in membranous septum	—	Yes	Incomplete right bundle branch block
5. R.T.	2 cm. in diameter; part of moderator band removed	Yes	Yes	Incomplete right bundle branch block
6. D.W.	Defect just above insert of tricuspid valve	Yes	—	Incomplete right bundle branch block
7. R.D. –.. ..	4 mm. in diameter; in muscular septum	—	Yes	Delayed activation of right ventricle
8. T.H.	12 mm. in diameter; defect in muscular septum	—	—	Delayed activation of right ventricle
9. T.S.	Defect just above membranous septum	—	—	Delayed activation of right ventricle
10. R.W.	2 by 0·25 cm.; above tricuspid valve	—	Yes	Delayed intraventricular conduction
11. C.D.	8 mm. in diameter; in membranous septum	—	Yes	Normal conduction.
12. J.H.	8 mm. in diameter; in base of pulmonary artery	—	—	Normal conduction
13. M.O.	7 mm. in diameter; high defect	—	—	Normal conduction

of the *R* wave in lead V_5 and the *S* wave in lead V_1. The average decrease was 15 mm. (1·5 mv.). This change was seen in eight patients. The changes in the voltage of *QRS* components over the right precordium during the second week were not enough to alter the previous diagnoses of right ventricular hypertrophy.

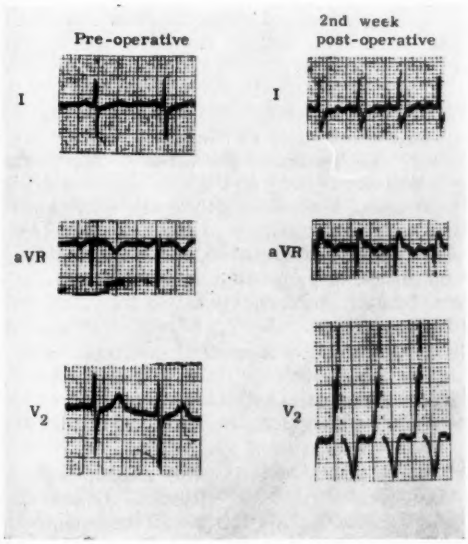

FIGURE IV

Pre-operative and post-operative tracings of a patient who had a ventricular septal defect. Note the predominant *QRS* changes during the final 0·04 second

An *rSR'* pattern over the right precordium was present in four cases prior to surgery. The *QRS* complex duration was 0·09 second or less in these records.

After the repair, the duration of the *QRS* complexes increased in 10 cases. The average increment was 0·03 second (range 0·01 to 0·05 second). The resulting configurations of the *QRS* complexes are listed in Table I.

The changes in eight cases were in the second portion of the *QRS* complex, the first 0·04 second remaining unaltered. The axis in the frontal plane moved to the right in six of these cases, with the development of a tall late *R* wave in lead aVR and a deep. wide *S* wave in lead I (Figure IV).

THE S-T SEGMENT

Atrial Septal Defect.—The *S-T* segments in the pre-operative tracings were unremarkable, except for two patients who showed a slight depression of this segment (0·5 mm. or less) in several leads. The records of all patients showed an elevation of the *S-T* segments after surgery. This was most often seen in leads II, III and aVF.

Ventricular Septal Defect.—The pre-operative records disclosed a depression of the *S-T* segment (0·5 to 1·0 mm.) in several leads in three cases, and an equivalent elevation of the *S-T* segment in six other cases. All but two patients showed an elevation of the *S-T* segment after surgery. This change was most frequently observed in the limb leads.

The post-operative elevation of the *S-T* segments was usually maximal on the first or second day after surgery. The average elevation was slightly less than 1·0 mm. The *S-T* segment returned to normal at different times in the various cases. This reversion occurred

from three to 14 days after operation. The amount of the *S-T* elevation during the first week after surgery is summarized in Figure V.

The T Waves

The mean frontal *T* wave axis moved to the right (with an average change of +28°) in nine patients after the repair of an atrial septal defect. After the repair of a ventricular septal defect, the *T* axis moved to the right in five patients and to the left in eight patients. The precordial *T* waves were generally unremarkable

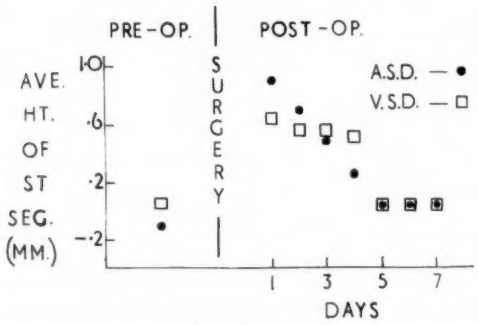

FIGURE V

Elevation of the *S-T* segment following the repair of defects of the atrial and ventricular septa

prior to the repair of either an atrial or ventricular septal defect. These *T* waves were frequently inverted after surgery. The most striking inversions were most often noted in the mid-precordial leads. The *T* wave changes are seen in Figures III and IV.

The Q-T Interval

Prolongation of the *Q-T* interval (0·44 second or greater) was present in one patient from each of the two groups prior to surgery. After operation, there was a prolongation of similar magnitude in two patients after the repair of an atrial septal defect and in three patients after the repair of a ventricular septal defect.

DISCUSSION

The Arrhythmias

There is no definite proof of the cause of the different types of supraventricular arrhythmias which occurred at varying intervals after the repair of an atrial secundum defect. Some workers have mentioned that these arrhythmias can occur without warning from three days to eight months after surgery. They postulate the occurrence of irritable foci developing during the healing of traumatized atrial tissue (Sasaki *et alii*, 1958). As a corollary, one might also expect to see evidence of irritable ventricular foci developing after the repair of a ventricular septal defect. However, the appearance of a ventricular premature beat or other evidence of such irritability after surgery was only a rare finding in this study.

Traumatic pericarditis may be advanced as a possible ætiological factor; and yet evidence of pericarditis is also present after the repair of a ventricular septal defect without the development of similar arrhythmias. Post-operative changes in electrolyte balance should also be considered. Heinz and Hultgren (1957) have referred to a diminution of intracellular potassium as a possible cause of atrial fibrillation following mitral valvotomy. Although such electrolyte disturbances could play a role in the arrhythmias of the early post-operative period, they could not explain the supraventricular arrhythmias following many months after the repair of an atrial defect which are described by Sasaki.

The ventricular fibrillation noted during or immediately after the repair of a ventricular septal defect was probably due to one of the immediate effects of surgery. Direct trauma to the ventricles and/or a sudden electrolyte imbalance merit consideration. Gordon and Jones (1959) have experimentally studied the varied means of inducing ventricular fibrillation in dogs. It is their conclusion that a rapid and severe ionic imbalance initiated by excess serum potassium is the most likely explanation of ventricular fibrillation after open heart surgery. As a possible corollary of this, Houssay (1937) has studied and described the release of large quantities of potassium from the liver as a secondary effect of anoxia, stress, reflex responses or hæmorrhage.

P Waves.—It is clear from these studies that there are definite *P* wave changes after the repair of an atrial ostium secundum defect to a degree not seen after the repair of a ventricular septal defect.

There are several possible explanations for this phenomenon. Pericardial inflammation may be a factor. A decrease in the height of all the *P* waves in an electrocardiogram has been noted as a consequence of pericardial inflammation (Lepeschkin, 1951). The interposition of fluid or the deposition of fibrin presumably exerts a dampening effect on voltage. However, although patients with repair of both a ventricular septal defect and an atrial septal defect showed evidence of pericarditis, only those who had the repair of an atrial septal defect experienced a major diminution in the height of the *P* waves. A diminished size of the

right atrium may be related to the *P* wave changes. It is known at surgery that the elimination of the left to right shunt during the repair of an atrial septal defect causes a diminution in the size of a previously dilated right atrium (Gerbode, 1958). If the tall *P* waves were due to an enlargement of the right atrium, then a decrease in the height of these waves would be a logical consequence of this surgery. There is evidence that the tall *P* waves (initially noted in these patients) are associated with atrial enlargement. Pre-operative cardiac catheterization studies showed that four patients had a pulmonary flow which was more than three times the systemic flow. These patients also had *P* waves in lead V_2 which were described as being " tall and peaked ". Those patients with less than a threefold increase in flow had *P* waves which were described as being normal. Martins de Oliveira and Zimmerman (1958*a*) have also noted that the incidence of tall peaked *P* waves increased in proportion to the magnitude of the left-to-right shunt. They observed (1958*b*) a tendency of the *P* axis to deviate to the left and backward after the repair of an atrial septal defect. They postulated that this was due to a reduction in the overloading of the right chambers.

A marked decrease in the height of *P* waves following the repair of isolated pulmonary stenosis has been reported (Landtman, 1954). This could reasonably be attributed to the same mechanism of diminished pressure within the right atrium and decreased right atrial size.

It is, therefore, most likely that the decreased height of the *P* waves after surgery is secondary to the smaller size of the right atrium after the closure of the shunt of blood through the atrial septal defect.

There was a small decrease in the *P-R* interval after the repair of an atrial septal defect in this series. It may be related to a decrease in the size of the right atrium with a resultant shortening of the conduction time. Macruz *et alii* (1958) have presented evidence to support the theory that a lengthened *P-R* interval follows right atrial enlargement because of an increased transit time of the electrical impulse across the atrium.

The QRS Complex

A shortening of the *QRS* complex duration was seen after operation in four of 10 patients who had an ostium secundum defect. This may have been due to diminished overloading of the right ventricle.

There was a prolongation of the *QRS* segment after the repair of a ventricular septal defect. Damage to the right bundle has been postulated as a cause of this increase (Deucher and Muir, 1959), and, indeed, a type of right bundle branch block appeared in six patients of this series after the repair of a ventricular septal defect. Two others developed delayed activation of the right ventricle.

The course of the right bundle has been studied extensively in normal hearts (Keith and Black, 1906 ; Walls, 1945 ; Glomset and Birge, 1945 ; Kistin, 1949) and in hearts with congenital defects (Reemtsma and Copenhaver, 1958). It has been shown that the common bundle begins near the central fibrous body deep to the insertion of the tricuspid ring and inferior to the coronary sinus. The downward course of the common bundle is altered in hearts with certain congenital defects. Reemtsma *et alii* (1958) have shown that the common bundle lies subendocardially along the postero-inferior margin of the membranous septal defects. The left and right bundle next branch at the inferior margin. The right bundle remains a single relatively discrete structure, which can be more easily interrupted than the left bundle, which arborizes diffusely.

Widran and Lev (1951), in tracing the right bundle inferiorly, have shown it to be close to the muscular bundle of Lancisi and the crista supraventricularis. Three patients of this series who had an infundibulectomy (which usually includes partial excision of the crista) showed a type of right bundle branch block after surgery. The occurrence of a right bundle branch block pattern after the repair of pulmonary infundibular stenosis has been previously reported (Zimmerman *et alii*, 1958 ; Hanson, 1958). Zimmerman's group performed studies to elucidate this phenomenon. They monitored the electrocardiographic response following resection of the infundibulum of the right ventricle in five dogs. They noted that in four of these dogs the changes resembling a right bundle branch block occurred only as the surgical damage involved the crista supraventricularis. They concluded that the electrocardiographic changes resembling a right bundle branch block might be due to interruption of the right bundle in some cases, but were more likely due to a change in activation of the heart from the area of the crista.

It is of interest that we have observed a patient who had a repair of a valvular stenosis and resection of an infundibular stenosis, and who did not develop right bundle branch block. The hypertrophied muscle in this particular case was cut away in two channels laterally without damage to the crista. Other patients

who had undergone the resection of an infundibular stenosis and who subsequently showed right bundle branch block had a resection of tissue which was superior to the outflow tract, with resultant opportunity for encroachment upon the crista.

Gross dissection studies have shown that, as the right bundle moves inferiorly from the region of the crista, it becomes once again relatively superficial in its terminal third, where it may end in the moderator band (Figure VI).

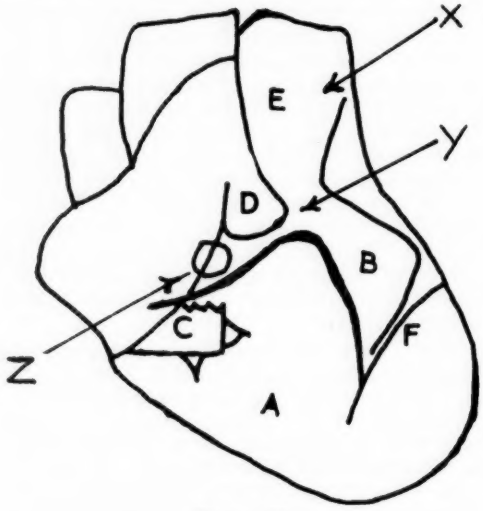

FIGURE VI

Diagram of right ventricle (A), showing the position of defects from Table I in relation to the right bundle branch B. This conduction pathway commences above the tricuspid valve C. It may approach an hypertrophied crista D, which is part of a stenosis of the infundibulum of the pulmonary outflow tract E. The right bundle usually ends near the moderator band F. X, high defects, Cases 12 and 13, no change in *QRS* complex. Y, infundibulectomy, Cases 1, 5 and 6 (three cases of right bundle branch block). Z, defect near or in membranous septum, Cases 1 to 7, 10 and 11 (six cases of right bundle branch block)

One of the patients in our series had a partial resection of the moderator band and was found to have a right bundle branch block pattern after surgery.

A branch of the anterior descending coronary artery was ligated in another patient, who was later found to have a right bundle branch block. A monitoring electrocardiogram disclosed no change immediately after the interruption of this vessel, so that the two events were probably not related. However, it is worthy of comment that James and Burch (1958) have shown that the major vascular supply to the interventricular septum is derived from the anterior descending coronary artery. Damage to this vessel could result in damage to conduction pathways through the septum.

The main change in the *QRS* vector direction in most of the patients who had a prolonged duration of the *QRS* complex after surgery occurred after the first 0·04 second of the complex with a rightward rotation of the later portions of the *QRS* complex. This would suggest that the first portion of the complex had already been inscribed before the surgically induced block was encountered.

Electrocardiographic evidence of right ventricular hypertrophy was present before surgery in seven of the 10 patients with an atrium secundum defect, and in five of 13 patients with a ventricular septal defect. The findings of right ventricular hypertrophy remained through the second week after operation, although there was some diminution in the height of *R* waves in right precordial leads. We would expect a pattern of hypertrophy to regress only over a prolonged period of time after the correction of hæmodynamic abnormalities. There was a large post-operative decrease in the sum of RV_5 and SV_1 in eight of 13 patients studied after the repair of a ventricular septal defect. This finding may be due to inflammatory changes imposed between the left ventricle and the chest wall, or there may have been a shift in the position of the heart within the thoracic cavity. It is doubtful whether this decrease in voltage could represent a diminution in the thickness of the left ventricular wall just two weeks after the elimination of the shunt.

S-T Segments

The finding of *S-T* segment elevation, which occurred after surgery, and which lasted for three to 14 days after the operation, confirms the presence of pericarditis in almost all these cases. This is not difficult to accept, in view of the trauma which this type of surgery entails.

T Waves

The changes in the mean frontal *T* wave vector would suggest that the repolarization of the ventricles is altered in a relatively uniform fashion after the repair of an atrial septal defect. Nine out of the 10 patients showed a rightward rotation of the mean frontal *T* wave vector. The lack of a consistent *T* wave vector shift after the repair of a ventricular septal defect may be interpreted as showing that the repolarization is affected in a variety of ways after operation on the ventricle.

The areas of symmetrical inversion of the precordial *T* waves after operation probably reflected many factors, including myocardial injury and ischæmia. There were no appreciable differences among the records of patients who had the repair either of an atrial defect or of a ventricular septal defect.

ACKNOWLEDGEMENTS

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A Review Written by Request

CURRENT VIEWS ON BLOOD COAGULATION AND HÆMORRHAGIC DISORDERS [1]

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FLUIDITY of blood and hæmostasis depend on three mechanisms which normally prevent intravascular thrombosis and an hæmorrhagic tendency. The mechanisms are intravascular blood coagulation, extravascular or tissue hæmostasis and the vascular component. Much is known about the first two, but very little about the third.

Clinical examination and laboratory tests are complementary, and both are essential for the diagnosis of an hæmorrhagic condition and the assessment of the hæmostatic state of a patient. The value and limitations of each must therefore be known.

Clinical examination gives, in general, a satisfactory indication of hæmostatic activity, but little information about the nature of the disorder. Laboratory tests give an indication of the nature and intensity of a clotting defect, but not necessarily of the hæmostatic state. For example, not infrequently patients who bleed excessively give normal results in laboratory tests. It is possible that the tests are not sensitive enough, or that the bleeding is due to vascular factors which are not accessible to the tests. On the other hand, there are patients who, on clinical examination, are not suspected of defective hæmostasis, but who bleed excessively after minor trauma, tooth extraction or tonsillectomy. Laboratory tests may show in such cases clotting deficiencies.

It is established that more than a dozen blood components, some acceleratory, some inhibitory, in addition to vascular factors are required for efficient hæmostasis and maintenance of blood fluidity in man. It is one of the puzzles of nature that such a large number of independent components should be required. It is also established that, with one exception, deficiency of any component of the hæmostatic mechanism can lead to excessive bleeding.

The interaction of a large number of clotting factors must take place in a certain order. The sequence has not yet been fully established. It seems, therefore, premature to present a definitive scheme of blood coagulation at the present state of knowledge. Nevertheless, it is advisable for the purpose of presentation to divide the clotting process into stages. In the first stage thromboplastin is formed, in the second thrombin is formed, and in the third fibrin is formed. These stages may be depicted as shown in Figure I.

In this review, the clinical significance of the various clotting factors will be considered. They have some properties in common, and these will be discussed before a more detailed analysis of their individual properties is made.

COMMON PROPERTIES OF THE CLOTTING FACTORS

The plasma clotting factors are associated with alpha and beta globulins. Apart from fibrinogen with a concentration of 200 to 400 mg. per 100 ml., they are present in plasma in concentration only of the order of a few milligrammes per 100 ml.

Most of the clotting factors are produced by the liver, so that hepatotoxic substances reduce their synthesis. It is possible that other organs contribute to the formation in some degree. The site of production of factor VIII[1] (anti-hæmophilic factor) has not been elucidated. In contrast to most other plasma proteins, the clotting factors have a very short life in the

[1] Received on January 12, 1961.

[1] In the following discussion the nomenclature used is recommended by the International Committee for the Standardization of the Nomenclature of Blood Clotting Factors (Fantl, 1959).

circulation. When transfused, factor VIII has a half-life of a few hours, and fibrinogen of not more than four days (Gitlin and Janeway, 1960).

Deficiency of clotting factors may occur as a congenital abnormality, or may be acquired in pathological conditions. Compared with acquired hæmorrhagic disorders, those of congenital origin are rare. The congenital defects are permanent, but an acquired defect may be temporary. In a congenital defect the disturbance is more likely to be due to an inborn failure in the production than to excessive destruction. With the exception of alpha-hæmophilia and beta-hæmophilia, which are

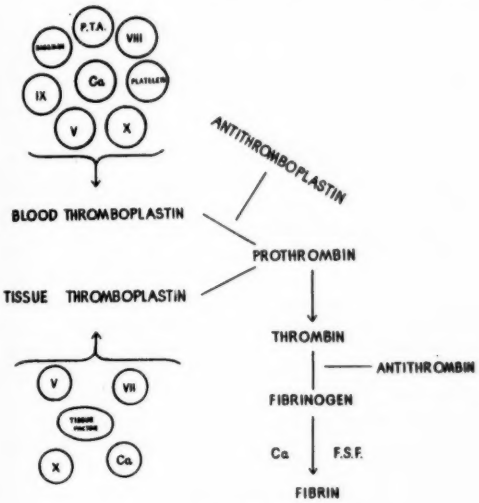

FIGURE I

mainly confined to the male, congenital deficiency of most clotting factors appear in either sex. In many instances, consanguinity of grandparents or parents is present and is thought to play a role in the appearance of the defect. Genetically, these congenital disorders vary from autosomal dominant to recessive sex linked.

Factor I (Fibrinogen)

Fibrinogen is the major plasma component influencing the erythrocyte sedimentation rate (E.S.R.), which is proportional to fibrinogen concentration. Elevation of plasma fibrinogen level is one of the most common non-specific responses to a number of unrelated pathological conditions and stimuli (Ham and Curtis, 1938). Fibrinogen levels are increased in pregnancy, in most infectious diseases, in myocardial infarction (Phear and Stirland, 1957), in rheumatic fever (Reid and Sproull, 1957) and after intravenous injection of typhoid vaccine. The amount of fibrinogen in plasma increases in people older than 40 years (Schulz, 1953).

Fibrinogen is converted into fibrin by the enzyme thrombin, a process which occurs in several steps. The fibrin molecules polymerize and form fibrils which align themselves and adhere to produce contractile strands. The fibrin clot enmeshes the formed elements of the blood and certain plasma components.

The literature lists about 30 cases of congenital fibrinogen deficiency. Two are recorded from Australia (Corbett, 1947; Wilson and Gutteridge, 1956). The defect is usually an isolated but a variable degree of thrombocytopenia is an associated finding. Hypofibrinogenæmia is one cause of difficulty in controlling bleeding from the umbilicus at birth. In afibrinogenæmia the blood is incoagulable and the E.S.R. is exceptionally low. Although no clot can form in the absence of fibrinogen, such patients may have long intervals of freedom from hæmorrhage. Apparently the formation of platelet plugs proceeds normally, and usually no petechial bleeding occurs because small lesions of blood vessels can be closed by the platelet plug. Therefore capillary fragility is not increased. Many of the clinical symptoms of afibrinogenæmia are similar to those observed in other bleeding tendencies, although bleeding into joints is rare. Brönnimann's (1954) patient had multiple cysts in the long bones.

Acquired hypofibrinogenæmia can result from reduced formation in malnutrition due to inadequate protein intake or severe liver damage and from shock (Ham and Curtis, 1938). In association with malignant disease of the prostate and pulmonary surgery, fibrinogen deficiency is usually secondary to abnormally high fibrinolytic activity. Another cause of fibrinogen depletion is connected with the defibrination syndrome. Experimentally, when thromboplastin enters the circulation, clotting occurs and fibrin is removed. If the thromboplastin infusion is continued, fibrinogen may be removed faster than it is formed and bleeding may occur. As placental tissue and amniotic fluid have thromboplastic activity, defibrination may be associated with premature separation of the placenta, amniotic fluid embolism or the intrauterine retention of a dead fœtus (Schneider, 1959). A different type of hæmorrhagic disorder is due to poor reactivity of fibrinogen with thrombin (Ingram, 1955).

Fibrinogen can be determined by chemical methods; but if the need is urgent the thrombin

clotting time of whole blood should be estimated with a potent thrombin preparation. Clotting occurs in a few seconds if fibrinogen is present. The chemical determination gives the amount of fibrinogen, but the fibrinogen may be qualitatively defective.

Fibrinogen concentrations below 100 mg. per 100 ml. of plasma are insufficient for hæmostasis and give erroneous results in several laboratory tests (Pinniger and Prunty, 1946). By contrast, it is not certain whether an increase in fibrinogen contributes to intravascular thrombosis. The treatment of hypofibrinogenæmia is transfusion of fresh plasma or stored plasma with a pH of 7·1 (Fantl and Marr, 1956) or isolated fibrinogen. There is a risk that with fibrinogen transfusion, infective hepatitis may be transmitted. Most patients tolerate multiple blood or fibrinogen transfusions, but Brönnimann (1954) reports that after several blood transfusions a strong antifibrinogen developed in a patient with congenital afibrinogenæmia.

Isolated fibrinogen may not survive very long in the recipient's circulation. The patient of Wilson and Gutteridge (1956) was treated with isolated fibrinogen, which was found to be ineffective. This patient was later given plasma transfusions, which produced a satisfactory fibrinogen level with a normal turnover rate (Fantl and Sawers, 1960).

Factor II (Prothrombin)

In addition to the dietary requirements for protein synthesis, vitamin K is essential for the production of prothrombin, but its role in this process is not known. Prothrombin is consumed in the clotting process, and normal serum contains only 10% or less of the amount in plasma. Bleeding can occur at levels below 25% of the normal concentration. Prothrombin deficiencies may be congenital, neonatal or acquired. The first is extremely rare (Borchgrevink *et alii*, 1959) but alleged hypoprothrombinæmia as part of the Münchhausen syndrome seems unique. It has occurred in this hospital (Fantl *et alii*, 1960).

The biological value of compounds with vitamin K activity varies according to the condition. In nutritional deficiency and obstructive jaundice, the natural vitamin K_1 can be replaced by simpler compounds—for example, menadione—but in prothrombin deficiencies induced by orally administered anticoagulants, vitamin K_1 and its derivatives are the only antidotes in the reversal of the hypoprothrombinæmia. The effect of vitamin K_1 should be apparent four hours later. If vitamin K_1 administration is not effective, inadequate liver function is indicated. In this instance prothrombin has to be supplied by fresh or stored blood or plasma transfusion, prothrombin being quite stable.

The prothrombin level in plasma is low in the first week of life; circumcision should therefore be carried out after this time. The success in raising the plasma prothrombin level of the newborn infant by administering vitamin K to pregnant women in labour or to the newborn baby depends on development of the baby. According to Bruijne (1960), vitamin K produced a normalization of the prothrombin time in most infants; but in babies with a highly prolonged prothrombin time on the first day of life in whom normalization was most desirable, vitamin K had no effect. Apparently in the latter cases inadequate liver function was responsible for the low prothrombin production.

The most common prothrombin deficiency seen today is induced by drugs of the coumarin and indandione series. They have no influence on circulating prothrombin, but inhibit prothrombin synthesis in the liver. Therefore the effect of the drug becomes appreciable only 24 to 30 hours after administration. Anticoagulant treatment has to be watched very carefully in tropical climates because of a rise in prothrombin time after prolonged sweating (Lyburn, 1959). Owing to hypersensitivity or to inadequate laboratory control, precipitous and dangerous hypoprothrombinæmia with fatalities has been reported on occasions (Fragge *et alii*, 1960; Smith, 1959; Payne, 1960; Wallace, 1960). Other drugs which depress prothrombin production are chloroform and salicylates (Quick and Clesceri, 1960). A combination of salicylates with coumarin drugs often produces synergistic effects in the depression of prothrombin. In addition to prothrombin, the drugs referred to above affect the clotting factors VII, IX and X. A reduction of thrombin and the three other clotting factors is also seen in vitamin K deficiency due to long-standing obstructive jaundice or steatorrhœa (Douglas, 1958) and to administration of antibiotics to babies (Sawers, 1958). The oral administration of anticoagulants during pregnancy should be carefully considered, because fœtal damage can be produced (Baker, 1960). The availability of the orally-administered anticoagulants to patients, nursing staff and the general public as rodenticides has led to the criminal use of these drugs and to self-inflicted hæmorrhagic disorders, especially among nurses (Verstraete and Vermylen, 1959; Fantl *et alii*, 1960).

Factor III (Thromboplastin)

Thromboplastin is necessary for the conversion of prothrombin into thrombin. Two types are recognized in the body. One is formed from blood components during clotting, and the other is liberated after damage to the cell. Blood thromboplastin is produced in a sequence of reactions involving Hageman factor, P.T.A., factor V, factor VIII, factor IX, factor X, platelets and calcium ions which require several minutes for completion. On the other hand, tissue thromboplastin, often produced in seconds, requires a tissue factor, factor V, factor VII and factor X for full activity. Absence of factor VII therefore leads to failure of tissue thromboplastic activity; but as factor VII is not involved in blood thromboplastin formation, there is no upset in the activity of blood thromboplastin in this condition. Plasma and serum can inactivate blood as well as tissue thromboplastin. Apart from thromboplastin activity, tissues contain materials which destroy clotting factors (Fantl and Ward, 1959). These principles, counteracting coagulation, may play some role in the prevention of extensive thrombosis induced by the thromboplastin activity.

The whole-blood clotting time of patients with malignant disease is often identical in glass and silicone containers. This may be due to the presence of tumour cells with thromboplastic activity.

Commercial thromboplastin preparations have been suggested for the treatment of hæmorrhagic disorders. They can be applied topically; but injections are dangerous and useless because, if they were effective, they would produce a defibrination syndrome.

Factor IV (Calcium)

Although exceedingly low concentrations of calcium are required for blood clotting, calcium is essential as an ion and also probably in bound form for the formation and action of the thromboplastins. Further calcium ions enhance the thrombin-fibrinogen reaction. Although pathological conditions in which the amount of calcium in blood could fall to a level inadequate for hæmostasis would be incompatible with life, and equally although abnormal hypercalcæmia does not produce thrombosis, the reduction of calcium ions, as by citrate in transfused stored blood, can be of clinical significance.

A possible connexion between massive transfusion of citrated blood and hæmorrhage has often been discussed. As a rule, even large volumes of citrated blood do not cause a significant fall of calcium ions in the circulation, because citrate is normally very rapidly metabolized. However, impaired liver function depresses utilization of citrate. If more than two litres of citrated blood are given in 20 minutes, it is recommended that 10 ml. of 10% calcium gluconate solution be injected for every litre of citrated blood transfused.

This problem has been dealt with by Hubbard *et alii* (1956), by Howland *et alii* (1957), and by Trobaugh and Cataldo (1959).

Factor V (Proaccelerin)

In plasma, factor V is labile. It is activated by thrombin to factor VI (accelerin—Ware *et alii*, 1948) and is consumed during clotting. Human serum is devoid of it. Factor V is necessary for the formation of blood thromboplastin and conversion of prothrombin in the presence of tissue thromboplastin.

Factor V deficiency occurs in a congenital (also called parahæmophilia—Owren, 1947) and an acquired form.

Acquired factor V deficiency has been observed in severe liver disease, sepsis, scarlet fever, polycythæmia vera, carcinoma of the prostate and tuberculosis. In some instances the bleeding tendency was of fatal severity.

Factor V deficiency can be corrected only by transfusion of fresh blood or fresh frozen plasma, for blood loses factor V activity during storage. The literature on factor V has been reviewed by Fantl (1957).

Factor VII (Proconvertin)

Factor VII is believed to be the precursor from which convertin, the active factor, is formed during the clotting process. It is a stable clotting factor and present in serum. Factor VII is not involved in the formation of blood thromboplastin, but it is essential for conversion of prothrombin with tissue thromboplastin.

In families with congenital factor VII deficiency, abnormal laboratory tests are often found in heterozygotes who do not have clinical symptoms of bleeding. In general it is a mild to moderate hæmorrhagic disorder. Two cases have been recorded in Australia (Hicks, 1955; Pitney, 1958).

Factor VII is deficient in the neonatal period. Reduction can occur in liver diseases (Cowling, 1956) and in vitamin K deficiency, and is characteristic after administration of drugs of the coumarin and indandione series (Douglas, 1955) and occasionally after propylthiouracil (Kolars and Gonyea, 1959). After administration of these drugs, the factor VII level is often reduced before that of prothrombin.

Vitamin K_1 has no effect on the congenital disorder, but is active in acquired factor VII deficiencies, if the liver is not severely damaged. In the congenital form, as well as in the case of vitamin K resistance, transfusions of fresh or stored blood, or of serum and the isolated factor have been used to raise factor VII levels. The effect lasts a few hours only (Hoag *et alii*, 1960). Increased factor VII activity is found in late pregnancy (Alexander *et alii*, 1956).

The fact that factor VII deficiency can cause excessive bleeding, and the observation that factor VII is essential only in the conversion of prothrombin with organ thromboplastins, provide evidence that for efficient hæmostasis two components, intravascular blood coagulation and tissue blood coagulation, are essential and complementary to each other.

The pertinent literature is reviewed by Alexander (1959).

Factor VIII (Antihæmophilic Factor)

Factor VIII activity is already within normal limits in blood in the neonatal period (Fantl and Ward, 1960; Jung, 1960). It has been suggested that factor VIII is produced by the reticulo-endothelial system (Pool and Spaet, 1954). As severe chloroform poisoning results in reduced factor VIII plasma activity (Penick *et alii*, 1958), it is possible that the liver is also involved. In this connexion it is worth pointing out that Sawers (1960) found normal factor VIII activity in a baby, aged 12 days, who had an hæmorrhagic disorder associated with fatal congenital virus hepatitis, despite the fact that the amounts of several other clotting factors were severely reduced.

Factor VIII is essential for blood thromboplastin formation. It is a labile material present in fresh blood and can be preserved for several weeks in citrated plasma at pH 7·1 stored at −20° C. or in the lyophilized form. Factor VIII is consumed in the clotting process, and therefore is absent from serum. It has been assumed that the formation of factor VIII is genetically determined and constant throughout life. However, Cooperberg and Teitelbaum (1960) find that the factor VIII activity in the plasma increases after the age of 40 years, and Pitney and Elliot (1960) reported that hyperglobulinæmia was associated with higher than normal factor VIII activity. Factor VIII in the plasma of normal persons varies from 60% to 200%. Deficient factor VIII activity is found in hæmophilia-A or alpha-hæmophilia. It is the most common hereditary hæmorrhagic tendency. It is often found that the factor VIII activity in plasma taken shortly after a transfusion contains a considerably lower activity than that calculated from mixtures prepared *in vitro*. It has been assumed that this is due to diffusion of factor VIII into the extravascular space, but it could be partly explained by inactivation in the circulation.

Although there are cyclic variations, according to intensity of the hæmorrhagic symptoms and laboratory tests, hæmophilics are grouped into severe, moderately severe and mildly affected bleeders. In general the clinical observations and the results of laboratory tests go parallel with the tendency to hæmorrhage. Severe hæmophilics have no detectable factor VIII activity in plasma, moderately severe hæmophilics have between 1% and approximately 5% factor VIII activity, and higher factor VIII concentrations (up to 60%) are found in mildly affected patients, who may show no excessive bleeding unless subjected to injury, tooth extraction or minor surgery. The activity of factor VIII is remarkably constant in a given pedigree of hæmophilics. The known distribution of alpha-hæmophilia in Australia is as follows: New South Wales, 130 (Kerr, 1960); Victoria, 115 (Fantl and Sawers, 1960); Queensland, 50 (Inglis, 1960); Western Australia, 43 (Pitney, 1960). The occurrence in this country is therefore approximately one in 10,000 males. The social problem is far greater than this number indicates. The problem of the female carrier of alpha-hæmophilia has attracted a great deal of attention. Some carrier women bleed excessively after injury, operations and childbirth. It would be desirable to know their factor VIII activity. Great variations have been found in the blood of female carriers (Nilsson *et alii*, 1960; Bentley and Krivit, 1960; Rapaport *et alii*, 1960). Most of the female carriers investigated by Nilsson *et alii* had a subnormal factor VIII activity. Pitney and Arnold (1959) find normal and low factor VIII concentration in the same pedigree.

Alpha-hæmophilia in the female can occur in homozygotes and heterozygotes (Fantl and Margolis, 1955). Nilsson *et alii* (1959) report alpha-hæmophilia in a "girl" with a male sex chromatin pattern. The occurrence of spontaneous alpha-hæmophilia is probably due to a high mutation rate, although investigations of heredity are of limited value in a population whose ancestors often cannot be traced beyond a few generations. Suggestions to avoid the occurrence of alpha-hæmophilia include grafting of normal factor VIII producing tissues into new-born alpha-hæmophilics (Fantl and Ward, 1960). Riis and Fuchs (1960) have determined the fœtal sex in suspected hæmophilia, and

suggest interruption of pregnancy if the fœtus is masculine. Many agents have been recommended for the treatment of hæmophilia, but only the transfusion of fresh blood or factor VIII preparations have stood the test. In the case of a hæmophilic requiring tooth extraction, fresh plasma and fresh-frozen plasma were found adequate even when the condition was severe (Fantl and Sawers, 1955; Arnold and Pitney, 1960). Fresh-frozen plasma was also adequate in major surgery on mild hæmophilics (Sawers, 1960*a*). Major surgery on severe hæmophilics or on hæmophilics who do not tolerate intravenous administration of large volumes of fluid has to be carried out under cover of transfusion with concentrates prepared from human plasma (Kekwick and Wolf, 1957; Blombäck and Nilsson, 1958). The difficulty in establishing and maintaining satisfactory hæmostasis in severe hæmophilics for any length of time with transfusion of plasma or plasma products has led to many suggestions to by-pass the blood-clotting system and make use of tissue hæmostasis. Unfortunately, none of the suggested ideas was found of any help.

Recently, the ingestion of peanuts has been suggested. Although it is admitted that they have no effect on the clotting process, it is held that peanuts contain a vasoconstrictor, and the hæmostatic effect is therefore related to blood-vessel response following trauma (Boudreaux *et alii*, 1960).

Pig and cattle plasma has a higher factor VIII activity than that of man. Potent animal preparations are available, but can be used only for a few days because of allergic reactions (Macfarlane *et alii*, 1957; Egeberg *et alii*, 1960).

Whereas alpha-hæmophilics have a normal skin bleeding time, another form of congenital hæmorrhagic disorder with a subnormal factor VIII activity is associated with prolonged skin bleeding time. It occurs in both sexes, and in the literature it is referred to as vascular hæmophilia, angiohæmophilia, pseudohæmophilia and von Willebrand's disease. However, not all patients have vascular anomalies (Horler and Witts, 1958). Nilsson *et alii* (1957) observed that fresh blood and plasma not only corrected the factor VIII deficiency, but also reduced the prolonged skin bleeding time. Again, this is not found in all patients of this group (Fantl and Sawers, 1960*a*). These inconsistencies make it doubtful whether all these patients had the same defect. It is therefore preferable to refer to von Willebrand's syndrome. In Australia, Pitney (1960) has investigated 23 patients with von Willebrand's syndrome, Fantl and Sawers (1960*a*) 5, and Kerr (1960) 3.

Factor IX (Plasma Thromboplastin Component, P.T.C.)

This factor occurs in plasma as a precursor which is changed into the active form during clotting. Serum contains very high factor IX activity.

The congenital form of factor IX deficiency is also called Christmas disease (Biggs *et alii*, 1952), hæmophilia-B or beta-hæmophilia. Clinically and genetically, beta-hæmophilia is very similar to alpha-hæmophilia in many respects. Laboratory tests clearly differentiate the two conditions.

The incidence of congenital factor IX deficiency is approximately 16% of the cases of hæmophilia reported in the literature. The known occurrence of beta-hæmophilia in Australia is: New South Wales, 32 (Kerr, 1960); Victoria, 21 (Fantl and Sawers, 1960*b*); Western Australia, 3 (Pitney, 1960).

Female carriers of beta-hæmophilia frequently show reduced factor IX activity in their plasma (Firkin, 1958). Congenital factor IX deficiency in the female has also been observed (Fantl and Sawers, 1960*c*).

Acquired factor IX deficiency can occur in liver dysfunction, and is common during treatment with anticoagulants given by mouth (Sise *et alii*, 1955).

In contrast to alpha-hæmophilia, beta-hæmophilia can be corrected temporarily by transfusion with stored blood and serum, and plasma, because factor IX is quite stable (Geratz and Graham, 1960). Factor IX has been reviewed by Aggeler (1957).

Factor X (Prower-Stuart Factor)

This blood-clotting factor is named after two patients who had a congenital bleeding tendency with a similar clotting defect (Telfer *et alii*, 1956; Graham *et alii*, 1957). Factor X is involved in blood thromboplastin formation, and is required for conversion of prothrombin in the presence of tissue thromboplastin or Russell's viper venom. Factor X is present in plasma and serum. It can be differentiated from factor VII by laboratory tests.

Factor X is reduced in liver disease and during oral anticoagulant treatment.

Plasma Thromboplastin Antecedent (P.T.A.)

P.T.A. is a clotting factor required for blood thromboplastin formation. It is present in plasma and serum and is quite stable during storage of blood.

The congenital deficiency has been observed in both sexes, and usually results in mild hæmorrhagic disorders; but recently Cavins and Wall (1960) found a serious bleeding tendency associated with P.T.A. deficiency.

In order to establish the clotting defect, it seems necessary to compare patient's plasma with authentic P.T.A.-deficient plasma.

Rosenthal (1957) has reviewed the relevant literature.

Hageman Factor

Laboratory tests carried out before an operation on a patient named Hageman showed abnormally long blood-clotting time; but his history gave no indication of a bleeding tendency.

In laboratory tests, Hageman factor is essential for the development of blood thromboplastin activity. Hageman factor is activated and adsorbed by glass (Margolis, 1958; Hardisty and Margolis, 1959). This explains the observation that shed blood clots in shorter time when in contact with hydrophilic than with hydrophobic surfaces.

Margolis (1960) found that Hageman factor is also involved in capillary permeability.

Patients with Hageman factor deficiency have suffered serious injuries and have undergone extensive operations without excessive bleeding (Fantl *et alii*, 1960). These facts indicate the shortcomings and difficulties of physiological interpretation of the results of laboratory tests carried out in glass or any other foreign material. A clearer picture will be obtained when clotting can be performed in containers with surface properties similar to those of a blood vessel. Hageman factor has been reviewed by Ratnoff (1960).

Fibrin-Stabilizing Factor (F.S.F.)

The clot formed in normal plasma is insoluble in concentrated urea solution, but fibrin prepared from purified fibrinogen and thrombin is soluble.

The insolubility of the plasma clot is due to calcium ions and to a plasma factor F.S.F. (Laki and Lorand, 1948). This factor is missing in serious disturbances in the metabolism of bone marrow (Lorand and Dickenman, 1955), and recently a hæmorrhagic disorder was found associated with a deficiency of F.S.F. (Duckert, 1960).

Hæmorrhagic disorders associated with deficiency of more than one clotting factor, both as congenital disorders and in acquired form, have been observed in a number of .nstances—for example, Bonnin *et alii* (1960).

Platelets

After blood is shed, one of the earliest changes detectable in platelets before visible fibrin formation is viscous metamorphosis, which takes place in several stages. First, adhesiveness or stickiness develops; this is followed by aggregation or clumping and fusion. Le Roy *et alii* (1960) found a thrombocyte-agglutinating factor in plasma. Hellem (1960) indicates that platelets in citrated blood are non-adhesive until a substance (factor R) is released from the red cells by contact with a foreign surface. These observations indicate that it is possible that more than one mechanism is operative in the early phases of platelet alteration. Platelet aggregation which is observed in normal blood should be distinguished from platelet agglutination; this is an immunological phenomenon due to anti-platelet factors which may be present in the serum of patients who have received blood transfusions or during pregnancy. Platelet agglutination is also found in some cases of thrombocytopenia (Garrett *et alii*, 1960). These platelet-agglutinating factors are probably immune iso-antibodies and are not present in normal human serum (Dausset, 1959). Patients who develop thrombocytopenic purpura as a result of sensitivity to some drug have in their serum a different antibody (Ackroyd, 1955).

Absence of viscous metamorphosis and platelet aggregation can be associated with a bleeding tendency. Sharp (1958) and Biggs *et alii* (1958) observed normal viscous metamorphosis in all severe hæmorrhagic conditions due to lack of plasma-clotting factors, with the exception of P.T.A. and Hageman factor deficiency. But Zucker and Borelli (1960) found viscous metamorphosis unimpaired in all the above-mentioned hæmorrhagic conditions. Increased adhesiveness of platelets is thought to occur in thrombotic conditions (McDonald and Edgill, 1959).

Any study of platelet alteration requires strict observation of details of procedure, for the lability of platelets and their adhesion to edges of a cut blood-vessel and to foreign surfaces within seconds make a standardization of the procedure difficult (Hugues, 1959).

Hæmorrhagic conditions which are characterized by platelets present in adequate numbers but lacking in one or more of the phases of viscous metamorphosis are grouped as thromboasthenia and thrombopathia (Braunsteiner and Pakesch, 1956). These conditions are associated with a prolonged skin bleeding time and increased capillary fragility. The

platelets are defective in enzymes involved in glycolysis (Gross *et alii*, 1960).

In general, hæmorrhage may occur when the platelet level falls below 100,000 per cubic millimetre of blood. Bonnin (1956) finds that the thromboplastic activity of platelets from patients with thrombocytopenia is qualitatively abnormal, and that their serum antagonizes the thromboplastic activity of normal platelets. Hæmorrhages may also occur when the number of platelets increases to over 1,000,000 per cubic millimetre, at which concentration the results of laboratory tests become abnormal. This is probably not related to platelet defect, but to the fact that an excess of normal platelets behaves as an inhibitor of blood coagulation (Nilsson *et alii*, 1960*a*).

Platelets participate in the clotting process by release of several substances. Platelet factor 3 is essential for the formation of blood thromboplastin (Seegers, 1956). Menorrhagia related to deficiency in a thromboplastic factor of platelets has been reported (Frazer, 1959).

After the clot is formed, platelets take part in clot retraction. Deficient clot retraction occurs in thrombocytoasthenia (Glanzmann-Naegeli) and polycythæmia. In the former case it is due to platelet abnormality, and in the latter to the increased bulk of the clot in the presence of normal platelets. Platelets are incorporated in the blood clot; but some breakdown products are present in serum (O'Brien, 1955).

A platelet is a miniature storehouse of biologically active components. In some ways it is comparable to a sponge which absorbs plasma proteins. Serotonin, also carried by platelets, is a powerful vasoconstrictor. For a long time it was considered to play an important role in hæmostasis; yet it is established that platelets freed of serotonin by treatment with reserpine do not differ from normal platelets in the coagulation process and clot retraction, nor do the patients so treated have a prolonged skin bleeding time or signs of an hæmorrhagic tendency.

Platelet factor 4 is another component which is connected with blood coagulation. This material can bind heparin and is therefore referred to as anti-heparin factor (Deutsch *et alii*, 1957). Platelets are also a source of anti-fibrinolysin (Johnson and Schneider, 1953), and interfere with the lipæmia-clearing action of plasma after the injection of heparin (Mitchell, 1959).

One treatment for platelet deficiency is blood or platelet transfusion. Recent work has shown that only transfusion of fresh platelets increases the number of circulating platelets and has a hæmostatic effect (Baldini and Ebbe, 1960). In contrast to earlier reports, lyophilized platelets are of no value (Jackson *et alii*, 1959). It appears essential that the platelets should be transfused in the shortest possible time after blood collection and after the least possible handling. Direct blood transfusion has resulted in a number of instances in a rise of the number of platelets in the recipient (McLean, 1958). The success with which multiple platelet or blood transfusions maintain a certain platelet level in thrombocytopenia is very variable. This may be due to the existence of platelet groups. The transfusion of incompatible platelets would not result in a sustained rise in platelets (Ducos *et alii*, 1959; Dausset, 1959; Shulman *et alii*, 1960). Aas and Gardner (1958) found that transfused radioactive platelets disappeared immediately from the circulation and reappeared a day later. Tullis *et alii* (1959) noticed that transfusions resulted in an increase of platelets in the recipient greater than was expected. The lifetime of perfused platelets is eight to eleven days (Alfos *et alii*, 1959), and may be related to the patient's condition. It is difficult to evaluate the results obtained from blood or platelet transfusions, because Schulman *et alii* (1960) have shown that rises in the number of platelets after transfusion may be due to a plasma factor which stimulates the release of platelets from the megakaryocytes. Thrombocytopenia of some degree occurs in paroxysmal nocturnal hæmoglobinuria. It was suggested that the platelet in this condition may by lysed by the plasma hæmolytic system (Crosby, 1953); but Flexner (1960) finds no evidence for this hypothesis.

Inhibitors of Blood Coagulation

The amount of thromboplastin and thrombin formed during coagulation of blood is far greater than that required for the formation of fibrin. The excess of these compounds gradually disappears. This is due to the activity of antagonizing principles present in plasma and serum, which are called anti-thromboplastin (Spaet and Garner, 1955) and anti-thrombin respectively. These normally occurring inhibitors may prevent extensive intravascular coagulation and thrombosis; but their rate of action is very slow, in contrast to the fast reaction rate of thromboplastin and thrombin. Therefore these antagonists do not significantly influence normal hæmostasis. Several anti-thrombins (I to IV) occur in normal plasma and serum. No hæmorrhagic syndromes due to excess of antithrombins I to IV have been

recorded. Antithrombins V and VI occur in pathological conditions, and can cause bleeding. Antithrombin V has been found in the plasma of patients with rheumatoid arthritis (Loeliger and Hers, 1957) and gamma-myeloma (Fantl *et alii*, 1951; Verstraete and Vermylen, 1959). Antithrombin VI is formed as a breakdown product of fibrin or fibrinogen by plasmin (Kowalski, 1960). It may be present in plasma with pathological fibrinolysis. (For a review of antithrombins, see Soulier, 1959.)

Heparin is an inhibitor of several phases of blood coagulation. It is found in mast cells. Normally it is at most present in traces in circulating blood. A bleeding tendency due to heparinæmia has been described (Quick and Hussey, 1957). Breakdown of mast cells by nitrogen mustard liberates heparin into the circulation (Smith *et alii*, 1948).

Inhibitors may appear in the blood of persons who have shown no hæmorrhagic tendencies and have not received blood transfusions. The origin of these inhibitors has not been found. In the case of normal women who after an uneventful pregnancy carry clotting antagonists in their blood, it is possible that immunization against fœtal or placental antigen is responsible for the antagonist. The source which can produce the inhibitor in the male is not known. The potency of the antagonist varies from slight to very high, and it may be in the circulation from a few months to 11 years. Three cases of anticoagulants of this type have been recorded in Australia (Fantl *et alii*, 1951*a*; Collins, 1953). In severe cases, blood transfusions may be of no value in overcoming the inhibitory activity. The published cases in this group have been reviewed by Favre-Gilly and Thouverez (1959).

Anticoagulants as a result of multiple blood transfusions, both in alpha-hæmophilia and in beta-hæmophilia, have been observed in approximately 10% of patients (Munro and Jones, 1943; Lewis *et alii*, 1956; Biggs and Bidwell, 1959; van Creveld *et alii*, 1951; Fantl *et alii*, 1956). Specific inhibitors of prothrombin have been noticed in lupus erythematosus by several workers (see Bonnin *et alii*, 1956). Inhibitors against all other clotting factors have been observed (Soulier, 1959).

Conclusion

In the foregoing discussion, several important aspects have been neglected. In particular, the influence of diet on the coagulation process and its connexion with thrombosis has been omitted. The value and selection of laboratory tests for assessing hæmostatic efficiency or a predisposition to thrombosis have not been indicated. The role of fibrinolysis, its interference with hæmostasis and its connexion with thrombosis have not been mentioned. These important problems have not been included, for their discussion would have greatly lengthened this review and might have somewhat obscured the pattern of the coagulation process presented.

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